Chiral thiocrown ethers

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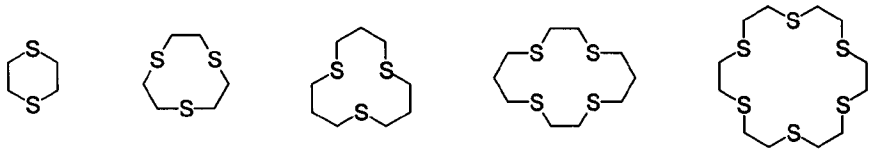
CHAPTER 2

SYNTHESIS OF BIS-β-NAPHTHOL DERIVED THIOCROWN ETHERS

2.1 *Introduction*

The history of thiocrown ethers goes back to 1886 when Mansfeld reported the synthesis of 1,4,7-trithiacyclononane (9S3).[1] At that time, except for cycloheptanone and cycloheptylamine, no molecules with ring sizes larger than six atoms were known. In an attempt to synthesize ring structures larger than 6 membered rings Mansfeld allowed 1,2-dibromoethane to react with sodium sulfide and isolated a product that he concluded to be 9S3. In a similar manner he synthesized 12S3 from 1,3-dibromopropane.



Scheme 2.1 *Several thiocrown ethers and their trivial names*

In 1920 Ray published the first of a series of papers on 9S3.[2] He reported that preparation of ethanedithiol by reaction of 1,2-dibromoethane with potassium hydrogensulfide provides 9S3 as a byproduct upon distillation. However, in contemporaneous work Bennett proved by molecular weight determination that the product Mansfeld and Ray found was in fact *p*-dithiane (6S2) and not 9S3.[3]

Therefore, actually, the history of thiocrown ethers goes back to 1934 when Meadow and Reid were the first to isolate a macrocyclic polyether compound containing only sulfur heteroatoms.[4] They allowed sodium ethanedithiolate to react with 1,2-dibromoethane to obtain a complex reaction mixture that contained cyclic poly-thioether compounds of different ring sizes and open chain poly-thioethers. From this mixture they isolated 1,4,7,10,13,16-hexathiacyclooctadecane (18S6, **2.3**) in 1.7% chemical yield.

More than 30 years later thiocrown ethers gained renewed attention when their potential ligating properties for transition metal ions was realized. In 1969 Rosen and Busch synthesized 14S4 (in 7.5% chemical yield) and prepared nickel(II) complexes of this tetradentate ligand.[5]

The main drawback for further exploration of thiocrown ethers was the lack of a general, high-

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1 Mansfeld, W. *Ber.* **1886**, *19*, 696.

2 a) Ray, P.C. *J.Am.Chem.Soc.* **1920**, *117*, 1090. b) Ray, P.C. *J.Chem.Soc.* **1922**, *121*, 1279. c) Ray, P.C. *J.Chem.Soc.* **1923**, *123*, 2174.

3 a) Bennett, G.M. *J.Chem.Soc.* **1922**, *121*, 2139. b) Bennett, G.M.; Berry, W.A. *J.Chem.Soc.* **1925**, *127*, 910.

4 Meadow, J.R.; Reid, E.E. *J.Am.Chem.Soc.* **1934**, *56*, 2177.

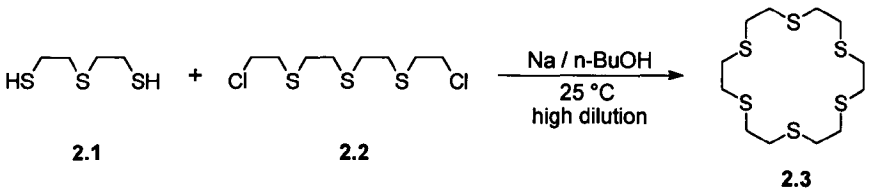
5 Rosen, W.; Busch, D.H. *J.Am.Chem.Soc.* **1969**, *91*, 4694.

yield synthetic route. In 1969 Black and McLean reported a greatly improved synthesis of 18S6.[6] They performed the same reaction as Meadow and Reid did, but applied high dilution conditions in ethanol. Under these conditions they claim to have synthesized 18S6 in 31% yield. However, this yield could not be reproduced by other groups. The groups of Cooper and Ochrymowycz independently found that the route described by Black and McLean affords 18S6 in no more than 8% yield.[7]

2.2 *General synthetic routes to thiocrown ethers*

2.2.1 *The sodium / n-butanol method*

A general problem encountered in the synthesis of macrocycles is the ring closure reaction of acyclic precursors. Methods had to be developed to circumvent the unfavorable entropy effects in forming a macrocylic system. After pioneering work on the synthesis of mixed oxo-thiocrown ethers by Pedersen[8] and Bradshaw[9], Ochrymowycz and coworkers were the first to systematically study the synthesis of thiocrown ethers containing only sulfur heteroatoms.[10] They were able to synthesize 18S6 in 33% yield by slowly adding dichloride **2.2** to a dilute solution of the disodium salt of dithiol **2.1** in n-butanol at room temperature (Scheme 2.2).



2.1 **2.2** **2.3**

Scheme 2.2 *Synthesis of 18S6 by Ochrymowycz et al.*

Several factors influence the yield and product distribution of this reaction. The concentration of the reactants influences the ratio of cyclic and linear (polymeric) products. In the first step of a reaction between an α,ω-dithiol with an α,ω-dichloride one thiolate reacts in a S_N2 manner with one chlorine atom giving α-chloro-ω-thiolate intermediate **2.4** (Scheme 2.3). This intermediate can react *intra*molecularly giving a cyclic product (**2.3**) or *inter*molecularly resulting in linear products. The linear intermediates **2.5** and **2.6** can react with another molecule **2.1** or **2.2** to give longer-chain α-chloro-ω-thiolates, which can either cyclize to larger ring thiocrown ethers or react with another open chain chloride or thiolate giving longer-chain α-chloro-ω-thiolates or α,ω-dithiolates. When the reaction is performed under high dilution conditions the formation of cyclic products will be favored.

The ratio of cyclic to linear product is also influenced by the type of leaving group. When a bromide is used instead of a chloride more cyclic product will be formed, i.e. intramolecular

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6 a) Black, D.St.C.; McLean, I.A. *Tetrahedron Lett.* **1969**, 3961. b) Black, D.St.C.; McLean, I.A. *Aust.J.Chem.* **1969**, *22*, 3961. c) Black, D.St.C.; McLean, I.A. *Aust.J.Chem.* **1971**, *24*, 1401.

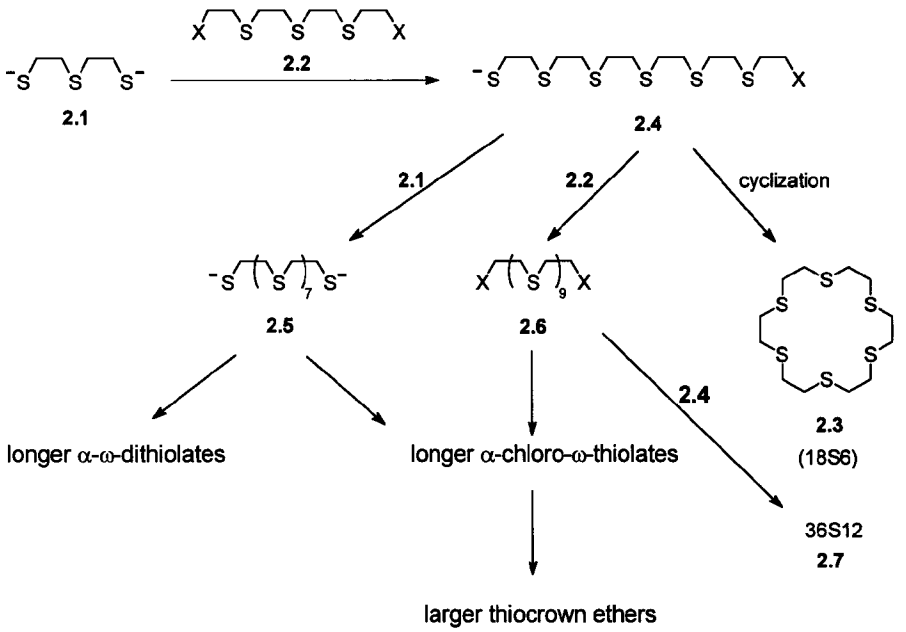
7 Cooper, S.R. *Acc.Chem.Res.* **1988**, *21*, 141.

8 a) Pedersen, C.J. *J.Org.Chem.* **1971**, *36*, 254. b) Pedersen, C.J.; Frensdorff, H.K. *Angew.Chem.Int.Ed.Engl.* **1972**, *11*, 16.

9 Review: Bradshaw, J.S.; Hui, J.Y.K. *J.Heterocycl.Chem.* **1974**, *11*, 649.

10 Ochrymowycz, L.A.; Mak, C.-P.; Michna, J.D. *J.Org.Chem.* **1974**, *39*, 2079.

reaction is favored over intermolecular reaction. Due to the enhanced leaving group ability of bromide compared to chloride, linear intermediate **2.4** (X=Br) will be more reactive. When high dilution is applied there is an increased chance of *intra*molecular reaction of **2.4** before *inter*molecular collision with another linear bromide or thiolate molecule can take place. However, when a chloride is used instead of a bromide, *larger* rings and polymeric materials will be formed. Compound **2.2** (X = Cl) and intermediate **2.4** (X=Cl) are less reactive than their bromide analogs. Due to this diminished reactivity the lifetime of **2.4** (X = Cl) in the reaction mixture will be relatively long. When **2.2** (X = Cl) is added to the reaction mixture at a constant



Scheme 2.3 *Products and side-products in the macrocyclization of 2.1 and 2.2 (X = Cl, Br)*

rate, the concentrations of both **2.2** (X = Cl) and **2.4** (X = Cl) in the reaction mixture will be relatively high, resulting in an increased chance of intermolecular reaction between these two compounds upon formation of **2.6** (X = Cl). The formation of longer chain linear intermediates is thus favored, finally resulting in the formation of larger ring thiocrown ethers or polymeric material.

2.2.2 *The cesium carbonate / DMF method*

In 1980 the method of Ochrymowycz was greatly improved by Buter and Kellogg by using cesium thiolates instead of sodium thiolates and by using dimethyl formamide (DMF) as solvent.[11,12] The

11 Buter, J.; Kellogg, R.M. *J.Chem.Soc., Chem.Commun.* **1980**, 466.
12 Buter, J.; Kellogg, R.M. *J.Org.Chem.* **1981**, *46*, 4481.

method consists of slow addition of an equimolar mixture of a dithiol and a dihalide in DMF to a suspension of Cs_2CO_3 in DMF.[13] Cs_2CO_3 readily deprotonates the dithiol giving a cesium dithiolate which is reasonably soluble in DMF. The dithiolate reacts with the dibromide to form a thiocrown ether. Due to the *in situ* formation of the cesium thiolate the concentration of reactants is kept low, favoring the macrocyclization over the polymerization. By this method macrocyclization can be achieved even under moderately dilute conditions.
The use of cesium salts seems to play an essential role in this method and the relatively high yields are attributed to the so-called "cesium effect" (see Section 2.3).
The Cs_2CO_3 / DMF method turned out to be a generally applicable synthetic route to thiocrown ethers. Thiocrown ethers and mixed thio-oxocrown ethers were now accessible in high yield (generally 70-90%). By this method 18S6 can be synthesized on multi-gram scale in 76% yield.[14]

2.3 *The cesium effect*

The cesium salts of weak organic acids are very effective nucleophiles in substitution reactions.[15] They often react extremely cleanly in S_N2-type reactions making them applicable in substitutions on asymmetric secondary halides, mesylates and tosylates with complete inversion of configuration.[16]
In intramolecular substitution reactions high yields are obtained with cesium carbonate as a base. When different alkali metal carbonates are used as a base in a macrocyclization reaction the yield increases with $Li_2CO_3 << Na_2CO_3 < K_2CO_3 < Rb_2CO_3 < Cs_2CO_3$.[11,12] This effect seems to be general in macrocyclizations with thiolates[11,12, 14], alkanolates, phenolates[17], carboxylates[18], tosylamides[19] and in the synthesis of highly strained cyclic compounds[20] and is known as the "cesium effect".
A related reaction is the cyclization of catechols with α,ω-ditosylates in the presence of an excess of solid alkali metal fluoride.[21] The fluoride anion is a sufficiently strong base to generate a good nucleophile for the formation of an ether bond. But also the cation plays an essential role in the ring closure, as the yield of cyclized product depends on the nature of the cation. The yield of cyclization increases with KF < RbF ≤ CsF. When LiF or NaF are applied no cyclization product is obtained at all.
The question arises why cesium has such a beneficial effect on macrocyclizations. This effect is not fully understood and a great deal of discussion has taken place in the literature. Several factors contributing to the cesium-effect will be discussed.
Alkali and alkaline earth metal ions may greatly facilitate the formation of oxacrown ethers in Williamson-type cyclic ether formation. This phenomenon, known as the "template effect", arises from complexation of the crown's precursor around the metal ion (see Scheme 2.5). In macrocyclization, loss of the conformational entropy due to internal rotations around the single

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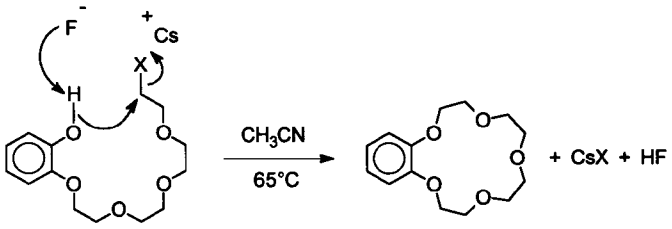
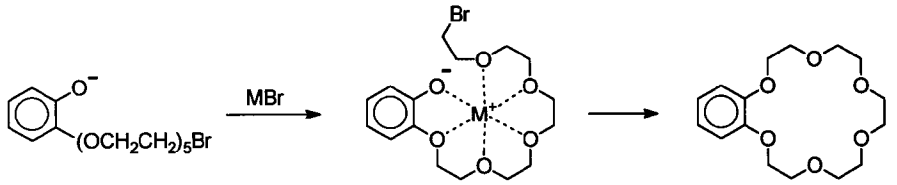
13 Buter, J.; Kellogg, R.M. *Org.Synth.* **1987**, *65*, 150.
14 Wolf, R.E. Jr.; Hartman, J.R.; Ochrymowicz, L.A.; Cooper, S.R. *Inorg.Synth.* **1989**, *25*, 122.
15 a) Gisin, B.F. *Helv.Chim.Acta* **1973**, *56*, 1476. b) Wang, S.-S.; Gisin, B.F.; Winter, D.P.; Makofske, R.; Kulesha, I.D.; Tzougraki, C.; Meienhofer, J. *J.Org.Chem.* **1977**, *42*, 1286.
16 Strijtveen, B.; Kellogg, R.M. *J.Org.Chem.* **1986**, *51*, 3664.
17 a) Van Keulen, B.J.; Kellogg, R.M.; Piepers, O. *J.Chem.Soc.,Chem.Commun.* **1979**, 285. b) Piepers, O.; Kellogg, R.M. *J.Chem.Soc.,Chem.Commun.* **1978**, 383.
18 Kruizinga, W.H.; Kellogg, R.M. *J.Am.Chem.Soc.* **1981**, *103*, 5183.
19 Vriesema, B.K.; Buter, J.; Kellogg, R.M. *J.Org.Chem.* **1984**, *49*, 110.
20 Vögtle,F.; Klieser, B. *Synthesis* **1982**, 294.
21 a) Reinhoudt, D.N.; De Jong, F.; Thomassen, H.P.M. *Tetrahedron Lett.* **1979**, 2067. b) Van der Ley, M.; Oosterink, H.J.; Hall, R.H.; Reinhoudt, D.N. *Tetrahedron* **1981**, *37*, 3661.



Scheme 2.4 *CsF assisted crownether synthesis by Reinhoudt et al.*

bonds of the crown's precursor provides a major contribution to the Gibbs energy of activation.[22] Reduction of the conformational entropy upon multiple coordination of the polyoxa chain with the metal ion should result in a greater "proximity" of the chain ends in the metal-associated chain than in the unassociated one .

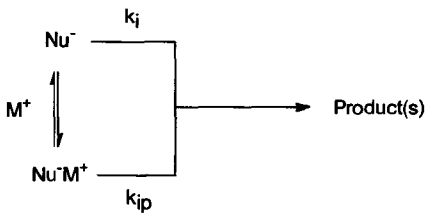


Scheme 2.5 *Template effect*

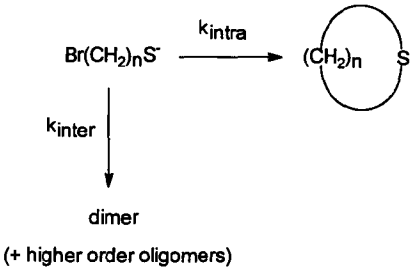
Alkali metal bromides (except LiBr) accelerate the ring closure of the tetramethylammonium salt of *o*-$HOC_6H_4(CH_2CH_2)_5Br$ to benzo-18-crown-6 (B18O6).[23] The acceleration is maximized when the metal ion fits exactly in the crown ether cavity. For B18O6 the acceleration of ring closure increases with $Na^+ < Cs^+ < Rb^+ < K^+$, whereas the acceleration of ring closure of the larger crown ether B21O7 increases with $Na^+ < K^+ < Rb^+ < Cs^+$.[24]
However, the cesium effect *cannot* be explained as a template effect because in ring closures to thiocrown ethers and other macrocycles the highest yields are obtained with Cs_2CO_3 as a base, *independent* of the ring size. Even the synthesis of the sterically overcrowded nine membered ring 9S3 with the Cs_2CO_3 / DMF method gives product in high (50%) yield[25], although the cesium ion is far too big to fit into the cavity of 9S3. The cyclization to 18S6 with Cs_2CO_3 gives the product in 76% yield, whereas cyclization with K_2CO_3 gives 18S6 in only 40% yield[12, 14], although K^+ better fits in the cavity of 18S6 than Cs^+. Furthermore even reactants that lack sufficient potential donor groups for Cs^+, and are therefore not capable of 'wrapping around' the metal center, readily yield macrocyclic products. For example the ring closure of long-chain α,ω-dithiols with long-chain α,ω-dibromides gives macrocyclic dithioethers in high yield when Cs_2CO_3 is applied as

22 a) Illuminati, G.; Mandolini, L. *Acc.Chem.Res.* **1981**, *14*, 95. b) Cacciapaglia, R.; Mandolini, L. *Chem.Soc.Rev.* **1993**, 221.
23 Illuminati, G.; Mandolini, L.; Masci, B. *J.Am.Chem.Soc.* **1983**, *105*, 555.
24 Mandolini, L.; Masci, B. *J.Am.Chem.Soc.* **1984**, *106*, 168.
25 Blower, P.J.; Cooper, S.R. *Inorg.Chem.* **1987**, *26*, 2009.

base, although only two donor groups for Cs^+ are present.[11,12]
Another example of a cesium effect is ring closure of 1,4-bis(chloromethyl)benzene with alkali metal to form [2ⁿ]paracyclophanes.[26] In this reaction no donor groups for coordination to the metal are present, excluding the possibility of a template effect. When metallic sodium is applied a mixture of larger ring paracyclophanes ([2^3] - [2^6]) is obtained, but with metallic cesium only [2^3]- and a little bit of [2^4]paracyclophane are formed, although both compounds are only obtained in low yields. In this reaction the cesium metal seems to favor trimerization, whereas sodium favors oligomerization.
All these examples clearly indicate that the cesium effect cannot be attributed to a template effect.
A cesium effect in nucleophilic substitution reactions suggests that there has to be an interaction between the nucleophile and the cesium ion. This interaction has to be different for the cesium ion as compared to the other alkali metal ions. Nucleophiles can react as free (Nu^-) or as cation-paired (Nu^-M^+) entities with independent kinetics: k_i for free ions and k_{ip} for ion-pairs (Scheme 2.6). On basis of a cesium effect one would expect i) the contribution to the overall rate of k_{ip} to be higher than k_i and ii) the k_{intra}/k_{inter} ratio (Scheme 2.7) for the ion-pair path to be greater than for the free ion path, namely $(k_{intra}/k_{inter})_{ip} > (k_{intra}/k_{inter})_i$, or at least greater than the corresponding values for



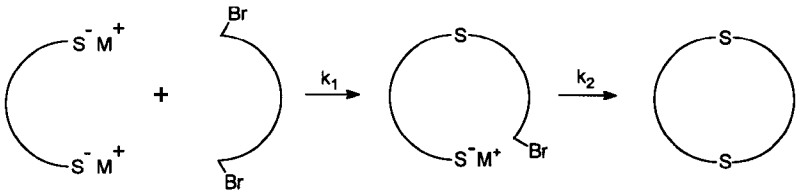
Scheme 2.6



Scheme 2.7

reactions with other alkali metal ions.[27] This implies that cesium salts of weak organic acids should have considerable ion-pair character in the reaction medium. However, ^{133}Cs NMR measurements showed that this is not the case in polar aprotic solvents like DMF and DMSO.[28] This means that the cesium effect cannot (solely) be explained in terms of ion-pairing phenomena.
An important contribution to the cesium effect lies in the solubilities of the alkali metal thiolates in DMF. The macrocyclization of a dithiol with a dibromide is a two stage reaction. In the first step the doubly charged dithiolate **2.8** couples with dibromide **2.9** giving the mono charged **2.10**, which can either cyclize or dimerize. The dimerization of **2.10** is competitive with its formation, i.e. both **2.8** and **2.10** can react with **2.9**. As a first approximation the reactivity per mole of **2.8** (two nucleophilic sites) is twice that of the mono charged ion (one nucleophilic site) **2.10**. To minimize dimerization it is desirable that the solubility of **2.8** be maximal so the competition for **2.9** will be more heavily in favor of doubly charged **2.8**, thereby decreasing the chance for dimerization of **2.10**. Cesium salts contribute positively here because of the higher solubilities of cesium dithiolates compared to other alkali metal dithiolates.[28] It is obvious that performing

26 Vögtle, F.; Kißener, W. *Chem.Ber.* **1984**, *117*, 2538.
27 Galli, C.; Mandolini, L. *J.Org.Chem.* **1991**, *56*, 3045.
28 Dijkstra, G.; Kruizinga, W.H.; Kellogg, R.M. *J.Org.Chem.* **1987**, *52*, 4230.



2.8 **2.9** **2.10**

Scheme 2.8 *Two stage cyclization to a thiocrown ether*

cyclizations under dilute conditions will also contribute positively to the macrocyclization/dimerization ratio. Under high dilution the rate of cyclization will be higher than the rate of dimerization. The concentration at which both rates are equivalent is called the effective molarity (EM). EM is defined by the ratio k_{intra}/k_{inter}.[29]
Another possible positive contribution of the cesium ion is its very large size (ionic diameter 3.3 Å), low charge/surface ratio (0.03 Z/Å^2) and high polarizability (2.9 Å^3) as compared to the other alkali metal ions: Li^+ (1.56 Å; 0.13 Z/Å^2; 0.03Å^3), Na^+ (1.96 Å; 0.085 Z/Å^2; 0.3 Å^3), K^+ (2.66 Å; 0.045 Z/Å^2; 1.1 Å^3) and Rb^+(2.98 Å; 0.035 Z/Å^2; 1.9 Å^3).[30] Because of these properties cesium ions form only weak ion pairs with thiolates (or other organic acids) resulting in exceptionally nucleophilic anions. This enhanced nucleophilicity ensures low concentrations of the charged intermediates **2.8** and **2.10** and therefore favors *intra*molecular reaction.
In conclusion it seems that the positive cesium effect lies in the enhanced solubility and nucleophilicity of the anions and not in ion-pairing phenomena.

2.4 *Synthesis of chiral thiocrown ethers*

In the past several decades many chiral oxocrown ethers[31] have been synthesized[32] derived from a variety of chiral compounds like tartaric acid[33], bis-ß-naphthol[34], sugars[35] and amino-acids[36]. Chiral *thiocrown* ethers are, however, an under developed area. Only few syntheses of chiral thiocrown

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29 a) Mandolini, L. *Adv.Phys.Org.Chem.* **1986**, *22*, 1. b) Galli, C.; Mandolini, L. *J.Chem.Soc., Chem.Commun.* **1982**, 251.

30 Lehn, J.-M. *Structure Bonding (Berlin)* **1973**, *16*, 1.

31 Crown ethers with solely oxygen heteroatoms in their cyclic backbone are named here *oxo*crown ethers as to distinguish them from *thio*crown ethers.

32 For a review see: Jolley, S.T.; Bradshaw, J.S.; Izatt, R.M. *J.Heterocycl.Chem.* **1982**, *19*, 3.

33 a) Dehmlow, E.V.; Knufinke, V. *Liebigs Ann.Chem.* **1991**, 1091. b) Behr, J.P.; Girodeau, J.M.; Hayward, R.C.; Lehn, J.M.; Sauvage, J.P. *Helv.Chim.Acta* **1980**, *63*, 2096. c) Anatanarayan, A.; Fyles, T.M. *Can.J.Chem.* **1990**, *68*, 1338.

34 a) Kyba, E.P.; Gokel, G.W.; De Jong, F.; Koga, K.; Sousa, L.R.; Siegel, M.G.; Kaplan, L.; Sogah, G.D.Y.; Cram, D.J. *J.Org.Chem.* **1977**, *42*, 4173. b) Cram, D.J.; Helgeson, R.C.; Peacock, S.C.; Kaplan, L.J.; Domeier, L.A.; Moreau, P.; Koga, K.; Mayer, J.M.; Chao, Y.; Siegel, M.G.; Hoffman, D.H.; Sogah, G.D.Y. *J.Org.Chem.* **1978**, *43*, 1930.

35 a) Stoddart, J.F. In *Synthetic Chiral Receptor Molecules from Natural Products, Progress in Macrocyclic Chemistry*; Izatt, R.M.; Christensen, J.J. Eds.; Wiley; New York, **1981**; Vol. 2, pp 174-220. b) Bako, P.; Fenichel, L.; Toke, L.; Davidson, B.E. *J.Chem.Soc.,Perkin Trans.I* **1990**, 1235. c) Bako, P.; Fenichel, L.; Toke, L. *Acta Chim.Hung.* **1984**, *116*, 323. d) Miethchen, R.; Gabriel, T. *Chem.Ber.* **1993**, *126*, 2309.

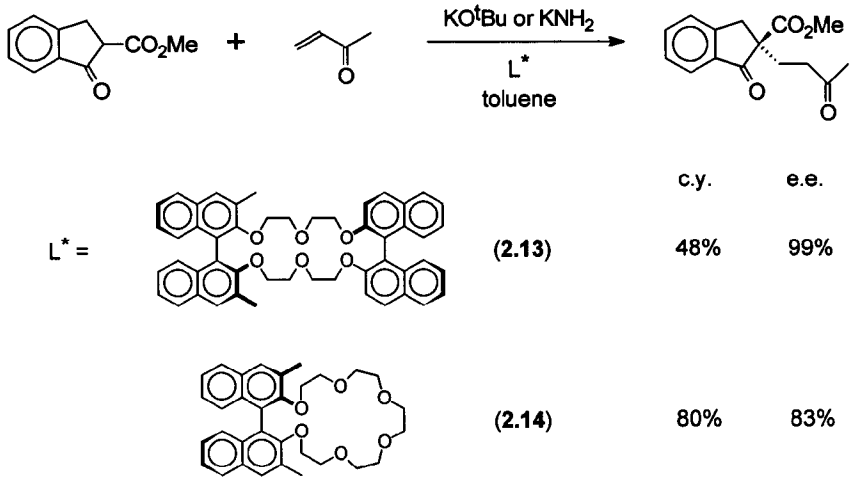
36 Chênevert, R.; Voyer, N. *Synthesis* **1985**, 981.

ethers have been reported in the literature, like tartaric acid derived thiocrown ether **2.11** and cysteine derived **2.12**.[37]

2.11 **2.12**

Scheme 2.9 *Chiral thiocrown ethers described in literature*

We were interested in chiral thiocrown ethers as potential ligands for asymmetric transition metal catalyzed reactions.



Scheme 2.10 *Asymmetric Michael addition with chiral crown ether ligands*

Among the most successfully applied chiral *oxocrown* ethers in asymmetric catalysis are the bis-ß-naphthol derived oxocrown ethers synthesized by Cram and coworkers.[38] Complexes formed by these oxocrown ethers with potassium amide (KNH_2) or potassium *tert*-butoxide (KO^{t}Bu) induce asymmetry in Michael additions. For example the reaction of methyl 1-oxo-2-indanecarboxylate with methyl vinyl ketone in the presence of the complex (*S,S*)-**2.13** / KO^{t}Bu gives the corresponding Michael adduct in 48% chemical yield and 99% e.e. (Scheme 2.10). When the mixture (*R*)-**2.14** / KNH_2 is applied the Michael adduct is formed in 83% e.e..[39]
Complexes of (*S*)- and (*R*)-**2.14** and (*S,S*)-**2.13** with KO^{t}Bu or butyllithium (BuLi) have also been

37 Vriesema, B.K.; Lemaire, M.; Buter, J.; Kellogg, R.M. *J.Org.Chem.* **1986**, *51*, 5169.
38 Kyba, E.P.; Siegel, M.G.; Sousa, L.R.; Sogah, G.D.Y.; Cram, D.J. *J.Am.Chem.Soc.* **1973**, *95*, 2691.
39 Cram, D.J.; Sogah, G.D.Y. *J.Chem.Soc.,Chem.Commun.* **1981**, 625.

used as initiators in the anionic polymerization of methacrylic acid esters.[40] Optically active helicoidal polymers are obtained with 80-90% isotacticity.
In view of these successful applications of bis-ß-naphthol derived oxocrown ethers we desired to synthesize sulfur analogs of these compounds. To synthesize the all-sulfur analogs bis-ß-thionaphthol was required as starting material. This compound can be obtained from bis-ß-naphthol in several steps.[41] However, the synthesis is very laborious and not very reproduceable, and the product is obtained in low yield. We therefore in first instance decided to synthesize mixed oxo-thiocrown ethers derived from bis-ß-naphthol rather than to synthesize the all-thio-analog derived from bis-ß-thionaphthol.

Table 2.1 *Ionic radii of several metal ions*[42]

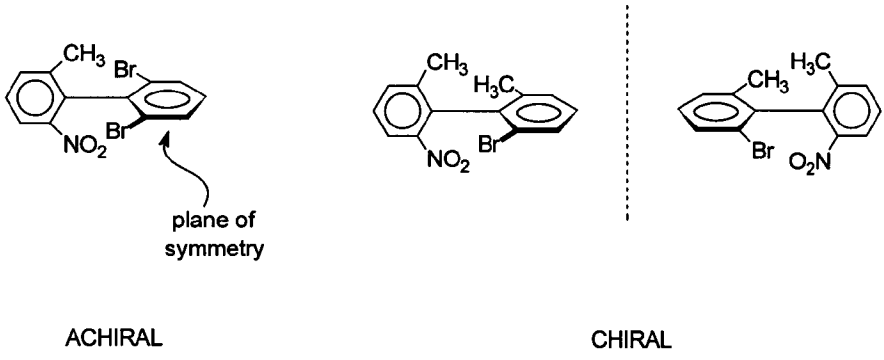
alkaline metal ion	ionic radius (Å)	transition metal ion	ionic radius (Å)
Li^+	0.68	Ni^{2+}	0.69
Na^+	0.97	Cu^+	0.96
K^+	1.33	Cu^{2+}	0.72
Rb^+	1.47	Zn^{2+}	0.74
Cs^+	1.67	Pd^{2+}	0.80
		Ag^+	1.26

An important feature of a crown ether is its cavity size. For optimal chelation of a metal ion the crown ether should just fit around the metal ion. In case of the oxocrown ethers 15crown5 just fits around the sodium ion, whereas 18crown6 just fits around the potassium ion. We wanted to synthesize thiocrown ethers for chelation of transition metal ions. From Table 2.1 it can be seen that the ionic radii of transition metal ions are in general smaller than the ionic radii of the alkaline metal ions.
So a thiocrown ether developed for chelating Cu^+ should have about the same cavity size as oxocrown ether 15crown5 (15O5), which just fits around Na^+. It should be noted that 15S5 has a smaller cavity size than 15O5, because sulfur atoms are larger than oxygen atoms.

2.5 *Bis-ß-naphthol, an axially dissymmetric biaryl system*

Biaryls containing substituents on the ortho-positions cannot freely rotate around the central single bond due to steric hindrance. The dihedral angle between the two aromatic rings in such compounds is larger than 0°. When either or both rings are symmetrical, the molecule has a plane of symmetry and the compound is achiral. However, if neither ring has a plane of symmetry the compound is chiral.
Those compounds that are chiral only because rotation around a single bond is prevented are

40 Cram, D.J.; Sogah, G.D.Y. *J.Am.Chem.Soc.* **1985**, *107*, 8301.
41 a) Cram, D.J.; Helgeson, R.C.; Koga, K.; Kyba, E.P.; Madan, K.; Sousa, L.R.; Siegel, M.G.; Moreau, P.; Gokel, G.W.; Timko, J.M.; Sogah, G.D.Y. *J.Org.Chem.* **1978**, *43*, 2758. b) Cossu, S.; Delogu, G.; De Lucchi, O.; Fabbri, D.; Fois, M.P. *Synth.Commun.* **1989**, *19*, 3431. c) Di Furia, F.; Licini, G.; Modena, G.; Valle, G. *Bull.Soc.Chim.Fr.* **1990**, *127*, 734. d) Fabbri, D.; Delogu, G.; De Lucchi, O. *J.Org.Chem.* **1993**, *58*, 1748.
42 *CRC Handbook of Chemistry and Physics*, 63rd ed., Editors: Weast, R.C.; Astle, M.J., CRC Press, Florida , **1983**.



Scheme 2.12 *Axially symmetric and dissymmetric biaryls (atropisomers)*

called atropisomers.[43] When the substituents on the ortho-positions are relatively small, or when only two or three ortho-substituents are present, rotation around the biaryl bond may not fully be prevented. In such cases optically active compounds can be prepared that slowly racemize on standing.[44]

The biaryl axis is the central bond in a very large number of natural products, including for example polyketides, terpenes, lignans, coumarins, flavonoids, tannins, peptides, and alkaloids.[45] Because of their interesting properties, not only as pharmacologically active natural products, but also for example as chiral reagents[46], chiral host molecules for inclusion compounds[47], chiral crown ethers[34], as the basis of chiral phases for chromatography[48], as chiral shift reagents[49], or as the basis of chiral liquid crystals[50] biaryls received considerable attention among synthetic chemists. Many syntheses of optically pure biaryls have been developed.[51]

The most thoroughly investigated and most widely applied member of the biaryl series is bis-ß-naphthol (**2.16**, Scheme 2.13). It has been extensively used as a chiral auxiliary[52] or as a chiral ligand[53] in a variety of asymmetric reactions. It is optically stable under neutral conditions and it

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43 For a review see: Oki, M. *Top.Stereochem.* **1983**, *14*, 1.

44 Stoughton, R.W.; Adams, R. *J.Am.Chem.Soc.* **1932**, *54*, 4426.

45 a) Torssell, K.G.B.; In: *Natural Product Chemistry*, Wiley, Chichester **1983**. b) Manitto, P.; In: *Biosynthesis of Natural Products*, Ellis Horwood, Chichester **1981**. c) Thomson, R.H.; In: *The Chemistry of Natural Products*, Blackie and Son, Glasgow **1985**. d) Cordell, G.A.; In: *Introduction to Alkaloids, A Biogenetic Approach*, Wiley, New York **1981**.

46 Noyori, R. *Chem.Soc.Rev.* **1989**, *18*, 187.

47 Weber, E, *J.Mol.Graphics* **1989**, *7*, 12.

48 a) Mikes, F.; Boshart, G. *J.Chromatogr.* **1978**, *149*, 455. b) Mikes, F.; Boshart, G. *J.Chem.Soc., Chem.Commun.* **1978**, 173.

49 Toda, F.; Mori, K.; Okada, J. *Chem. Lett.* **1988**, 131.

50 a) Yamamura, K.; Ono,S.; Tabushi, I. *Tetrahedron Lett.* **1988**, *29*, 1797. b) Yamamuro, K.; Ono,S.; Ogoshi, H.; Masuda, H.; Kuroda, Y. *Synlett* **1989**, 18. c) Gottarelli, G.; Hibert, M.; Samori, B.; Solladié, G.; Spada, G.P.; Zimmermann, R. *J.Am.Chem.Soc.* **1983**, *105*, 1318.

51 For a review see: Bringmann, G.; Walter, R.; Weirich, R. *Angew.Chem.Int.Ed.Engl.* **1990**, *29*, 977.

52 For example: a) Fuji, K.; Tanaka, K.; Mizuchi, M.; Hosoi, S. *Tetrahedron Lett.* **1991**, *32*, 7277. b) Fuji, K.; Tanaka, F.; Node, M. *Tetrahedron Lett.* **1991**, *32*, 7281. c) Fabbri, D.; Delogu, G.; De Lucchi, O. *Tetrahedron: Asymm.* **1993**, *4*, 1591.

53 For example: a) Hattori, K.; Yamamoto, H. *J.Org.Chem.* **1992**, *57*, 3264. b) Kaufmann, D.; Boese, R. *Angew.Chem.Int.Ed.Engl.* **1990**, *29*, 545.

has C_2-symmetry. When ligands are C_2-symmetric it does not matter from which side the substrate interacts with the ligand; the ligand then does not have the unwanted property of "sidedness".
Compound **2.16** can easily be synthesized as a racemate by oxidative coupling of 2-naphthol with $FeCl_3$ as an oxidant, either in solution[54] or in solid state[55]. Optically pure **2.16** has been obtained by resolution of the racemate[56], by enzymatic hydrolysis of a racemic diester derivative[57] or by asymmetric oxidative coupling of 2-naphthol[58].
Bis-β-naphthol is a white solid (mp 210 - 212 °C), which is optically stable at room temperature. Steric hindrance of the protons in the 8,8'-positions, and to a lesser extent the hydroxyl goups at the 2,2'-positions are responsible for the atropisomerism in bis-β-naphthol.[59] Racemization, at elevated temperatures, may occur through a *syn* inversion path, with close contacts of the hydroxyl groups at the 2,2'-positions and the protons at positions 8,8', or through an *anti* process in which positions 2,8' and 2',8 must pass by each other.

2.6 *Alkylation of bis-ß-naphthol*

In a retrosynthetic approach oxo-thiocrown ethers can be synthesized in two ways from bis-ß-naphthol, as depicted in Scheme 2.12.
The major disadvantage of path A is the use of ß-chlorosulfides, which are extremely toxic mustard gas derivatives. Furthermore higher reactivity is expected in path B, because thiolates are better nucleophiles than phenolates. We therefore chose path B.
Following path B, the first step will be alkylation of bis-β-naphthol. In the literature many methods have been described for alkylation of phenols. In general phenols can be alkylated by using a strong base and an alkyl halide. However, under (strongly) basic conditions racemization of bis-ß-naphthol occurs. Cram showed that enantiomerically pure bis-ß-naphthol is 69% racemized when it is stirred for 23 h in a 0.67 M KOH solution in n-butanol at 118°C and 72% racemized in a 1:1 mixture of dioxane and 20% aqueous HCl at 100°C, although it is optically stable under neutral conditions in dioxane-water at 100°C.[60] Under acidic or basic conditions both phenolic hydroxyl groups are charged and due to mutual repulsion the biaryl bond will be lengthened a little resulting in a diminished rotational barrier. Racemization under acidic conditions might also occur via the protonated keto-tautomer **2.17** (Scheme 2.13).
We wanted to develop a synthesis of bis-ß-naphthol derived thiocrown ethers starting with optically pure bis-ß-naphthol. In order to minimize racemization during the synthesis we searched for a mild alkylation procedure of bis-ß-naphthol.

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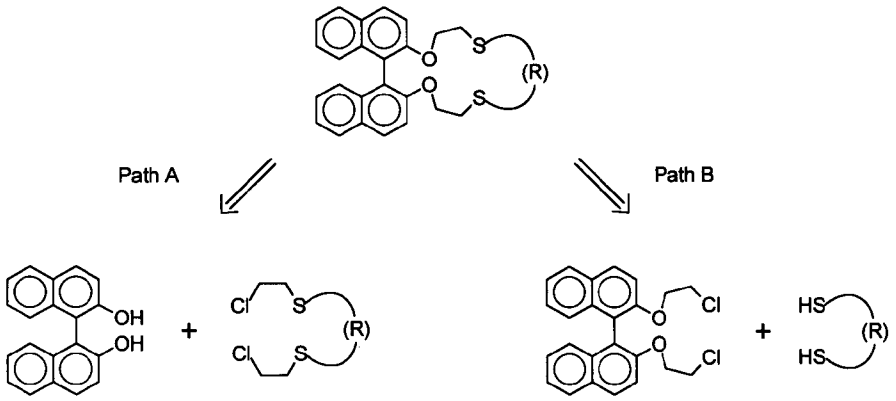
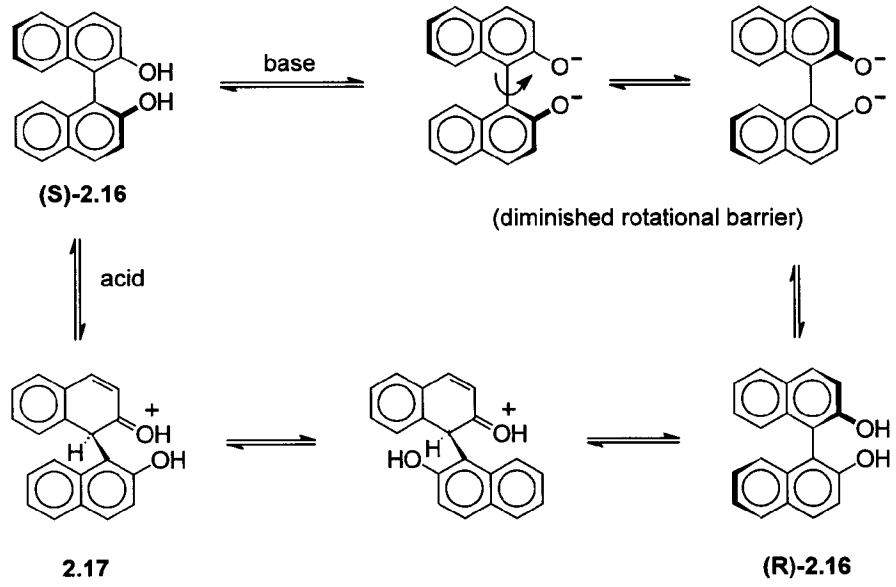
54 Pummerer, R.; Prell, E.; Rieche, A. *Chem.Ber.* **1926**, *59*, 2159.
55 Toda, F.; Tanaka, K.; Iwata, S. *J.Org.Chem.* **1989**, *54*, 3007.
56 a) Brunel, J.-M.; Buono, G. *J.Org.Chem.* **1993**, *58*, 7313. b) Fabbri, D.; Delogu,D.; DeLucchi, O. *J.Org.Chem.* **1993**, *58*, 1748. c) Tanaka, K.; Okada, T.; Toda, F. *Angew.Chem.Int.Ed.Engl.* **1993**, *32*, 1147. d) Gong, B.-Q.; Chen, W.-Y.; Hu, B.-F. *J.Org.Chem.* **1991**, *56*, 423. e) Tamai, Y.; Heung-Cho, P.; Iizuka, K.; Okamura, A.; Miyano, S. *Synthesis* **1990**, 222. f) Kawashima, M.; Hirayama, A. *Chem.Lett.* **1990**, 2299. g) Toda, F.; Tanaka, K. *J.Org.Chem.* **1988**, *53*, 3607. h) Jacques, J.; Fouguey, C. *Org.Synth.* **1988**, *67*, 1. i) Truesdale, L.K.; *Org.Synth.* **1988**, *67*, 13.
57 a) Miyano, S.; Kawahara, K.; Inoue, Y.; Hashimoto, H. *Chem.Lett.*, **1987**, 355. b) Kazlauskas, R.J. *J.Am.Chem.Soc.* **1989**, *111*, 4953. c) Kazlauskas, R.J. *Org.Synth.* **1992**, *70*, 60.
58 a) Brussee, J.; Groenendijk, J.L.G.; Te Koppele, J.M.; Jansen, A.C.A. *Tetrahedron* **1985**, *41*, 3313. b) Feringa, B.L.; Wynberg, H. *Bioorg.Chem.* **1978**, *7*, 397.
59 Kranz, M.; Clark, T.; Von Ragué Schleyre, P. *J.Org.Chem.* **1993**, *58*, 3317.
60 a) Kyba, E.B.; Koga, K.; Sousa, L.R.; Siegel, M.G.; Cram, D.J. *J.Am.Chem.Soc.* **1973**, *95*, 2692. b) Kyba, E.P.; Gokel, G.W.; De Jong, F.; Koga, K.; Sousa, L.R.; Siegel, M.G.; Kaplan, L.; Sogah, G.D.Y.; Cram, D.J. *J.Org.Chem.* **1977**, *42*, 4173.

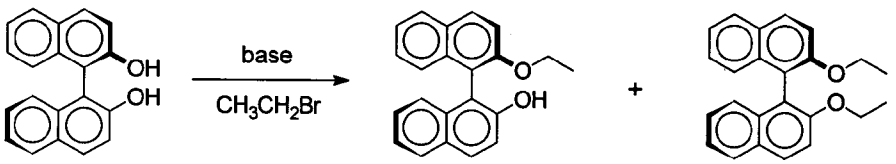


Scheme 2.12 *Retro-synthetic approach to bis-β-naphthol derived oxo-thiocrown ethers*



Scheme 2.13 *Acid and base catalyzed racemization of bis-β-naphthol*

In order to investigate the extent of racemization during alkylation under basic conditions we allowed bis-β-naphthol to react with ethyl bromide under a variety of conditions. Optically pure bis-β-naphthol (e.e. > 99.9%, determined by HPLC) was alkylated by stirring a mixture of one equivalent of bis-β-naphthol and four equivalents of ethyl bromide in the presence of three equivalents of base in different solvents. All reactions were carried out for 24 hours at the temperature



2.16 **2.18** **2.19**

Scheme 2.14 *Alkylation of optically pure bis-β-naphthol*

given in Table 2.1. The chemical yield was determined after workup. The ratio of mono- and bis-alkylated product was determined by ^1H NMR. The triplet for the CH_3-groups of **2.18** and **2.19** can be seen separately in the ^1H NMR spectrum. The ratio **2.18** / **2.19** can also be determined by integration of the ^1H NMR signals for the aromatic protons on C-8. These protons are seen separately from the other aromatic protons, and give a doublet at 7.97 (**2.19**) and 8.02 (**2.18**) ppm. The e.e. of the bis-alkylated product was determined by HPLC on a chiracel OT column.

Table 2.2 *Alkylation of bis-β-naphthol with ethylbromide*

entry	base	solvent	temperature (°C)	c.y. **2.18** (%)	c.y. **2.19** (%)	e.e. **2.19** (%)
1)	KO^{t}Bu	THF	66	-	94	98.6
2)	NaH	DMF	110	16	84	98.3
3)	K_2CO_3	acetone	56	5	93	99.6
4)	K_2CO_3	acetonitrile	82	-	100	99.0
5)	K_2CO_3	DMF	153	-	100	98.5
6)	K_2CO_3	DMF	110	-	100	99.6
7)	K_2CO_3	DMF	70	8	92	99.6

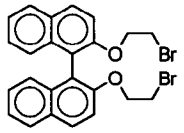
As can be seen from Table 2.2 hardly any racemization occurs under the applied reaction conditions. This is explained in terms of a short life-time of the bis-anion of **2.16**, i.e. the formation of mono-alkylated **2.18** must be fast. The mono-alkylated anionic intermediate does not racemize rapidly under basic conditions as follows from entry 2. After stirring for 24 hours at 110°C still 16% of **2.18** is present. If **2.18** were to racemize at the same rate as **2.16** (69% racemization in KOH/n-butanol at 118°C for 23 h[60]) the e.e. of **2.19** would be much lower than 98.3%.

In all cases highest e.e.'s were obtained when K_2CO_3 was used as base. The weak base K_2CO_3 probably deprotonates only one phenolic group at a time, whereas stronger bases like NaH and KO^{t}Bu readily deprotonate both phenolic groups simultaneously. The mono-anion of **2.16** has a less elongated biaryl bond compared to the bis-anion and therefore a higher rotational barrier, resulting in diminished racemization.

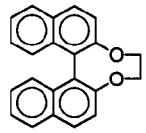
We conclude that, although the differences are only small, acceptable conditions for alkylation of optically pure bis-β-naphthol are the use K_2CO_3 as a base in DMF at 110°C.

2.7 *Synthesis of a bis-β-naphthol containing building block for thiocrown ether preparation*

Following path B in Scheme 2.12 we had to synthesize a bis-(2-halogenoethyl) derivative of **2.16**. Alkylation of **2.16** with 1,2-dibromoethane will probably not give the bis-(2-bromoethyl) derivative **2.20**, but cyclized product **2.21**.



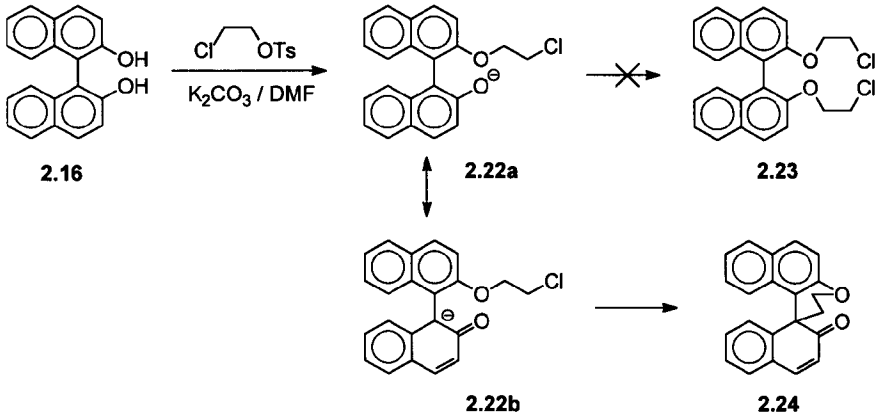
2.20



2.21

Scheme 2.15

Attempts have failed to synthesize **2.23** by alkylation of **2.16** with 1-chloro-2-tosyloxyethane under mild conditions (K_2CO_3 / DMF). We had hoped that substitution would take place of the more reactive tosylate, without substitution of the chloride. However, in addition to polymeric products, **2.24** was formed in 28% chemical yield. Cram and coworkers found the same product in reaction of ethylene glycol ditosylate with **2.16** in THF with KO^{t}Bu as base.[34a] However, when they performed the same reaction in DMF instead of THF they obtained **2.21** in 65% yield without detectable amounts of **2.24**. The solvent seems to play an essential role in product formation. In DMF the resonance structure **2.22a** (with a tosyl group instead of a chloride) is probably more important than **2.22b**, leading to formation of **2.21**. We, in our case, have an intermediate **2.22** with a less reactive chloride instead of a tosylate. This results in the thermodynamically favored alkylation via the more nucleophilic carbanion **2.22b**, leading to **2.24**.



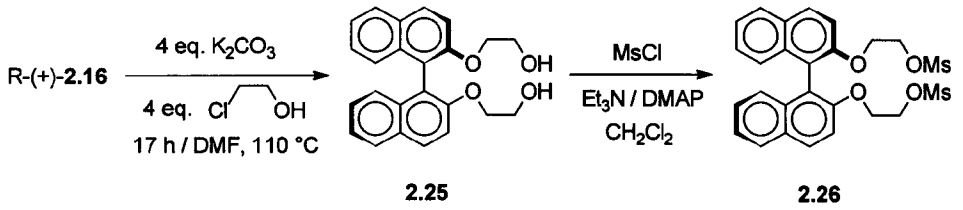
2.16 **2.22a** **2.23**

2.22b **2.24**

Scheme 2.16 *Reaction of bis-β-naphthol with 1-chloro-2-tosyloxyethane*

To circumvent these unwanted side reactions we alkylated **2.16** with 2-chloroethanol. In order to force the reaction to complete bis-alkylation we carried out the reaction with 4 equivalents of K_2CO_3 and 4 equivalents of 2-chloroethanol in DMF at 110°C for 17 h. The reaction was carried

out in the presence of 4-N,N-dimethylaminopyridine (DMAP) as a hypernucleophilic catalyst.[61] Bis-alkylated product was obtained in 81% yield. Bis-alcohol **2.25** was converted to its bis-mesylate **2.26** in 95% yield by reaction with mesyl chloride (MsCl).



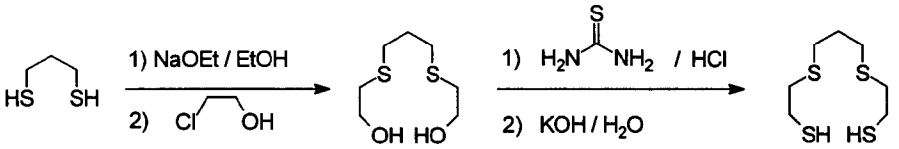
2.25 **2.26**

Scheme 2.17 *Synthesis of bis-mesylate* ***2.26***

When **2.16** was alkylated with THP-protected 2-chloroethanol the alkylation step was performed in a somewhat higher yield. Bis-(2-tetrahydropyranylethyl)-bis-β-naphtholate (**2.27**, not depicted) was obtained in 89% chemical yield. However, after deprotection with HCl the overall yield of **2.25** was comparable to the direct alkylation with unprotected 2-chloro ethanol.

2.8 *Synthesis of dithiols*

Bis-mesylate **2.26** can be converted to oxo-thiocrown ethers by cyclization with a dithiol. Only few (simple) dithiols are commercially available, like HS-$(CH_2)_n$-SH with n = 2-6, and bis-(2-mercaptoethyl)-sulfide. Other (more complex) dithiols have been synthesized from the corresponding diols or dihalides.



2.28 **2.29**

Scheme 2.18 *Elongation of dithiols via alcohol-thiol conversion*

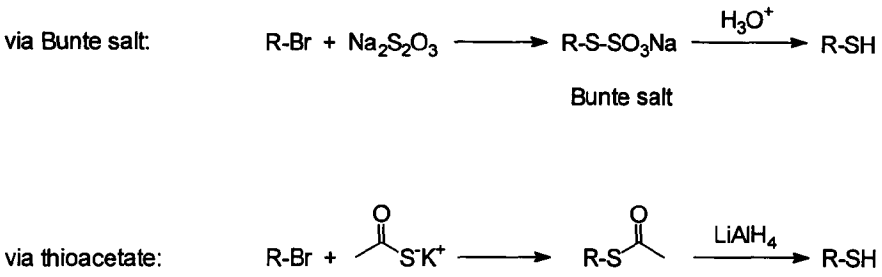
Alcohols can be converted to thiols by reaction with thiourea followed by hydrolysis of the formed isothioronium salt with KOH. By this method 1,3-propanedithiol has been converted to 1,4,8,11-tetrathiaundecane **2.29** by alkylation with 2-chloroethanol followed by reaction with thiourea (Scheme 2.18).[5]

(Di)thiols are readily converted to disulfides in the presence of an oxidant. Under basic conditions (di)thiols can be oxidized by oxygen via a radical coupling.[62] The conversion from diol to dithiol therefore should be performed under a nitrogen atmosphere in order to prevent oxidation to the

61 a) Scriven, E.F.V. *Chem.Soc.Rev.* **1983**, *13*, 129. b) Höfle, G.; Steglich, W.; Vorbrüggen, H. *Angew.Chem.Int.Ed.Engl.* **1978**, *17*, 569.

62 Wallace, T.J.; Schriesheim, A.; Bartok, W. *J.Org.Chem.* **1963**, *28*, 1311.

disulfide. When disulfides are formed they can be converted to dithiols by reduction with $LiAlH_4$. Dithiols can be synthesized from dihalides by a whole variety of methods. The most commonly used methods are via formation of Bunte salts[63], by reaction with thiourea[64] or by substitution with thioacetate followed by reduction[65]. Sterically hindered halides can be converted to thiols by reaction with potassium thiocyanate, followed by reduction[66], by reaction with disodium trithio-



Scheme 2.19 *Conversion of halides to thiols*

carbonate (Na_2CS_3) followed by reduction[67] or by reaction with sodium sulfide and sulfur, followed by reduction of the obtained disulfide[68].
A major problem in the synthesis of dithiols is the purification. In general dithiols are oils with high boiling points. Dithiols with relatively low boiling points can be distilled at reduced pressure, but often with a considerable loss of product. Distillation should be performed very fast, with a gas-flame, to minimize loss of product. Dithiols with higher boiling points or solid dithiols can be purified by column chromatography, but often dithiols are converted to disulfides on the column.

2.9 *Ring closure to thiocrown ethers*

Bis-mesylate **2.26** was cyclized with 1,3-propanedithiol using the Cs_2CO_3 / DMF method. Thiocrown ether **2.30** was obtained in 30% chemical yield (Scheme 2.20). Cyclization with other dithiols gave the thiocrown ethers depicted in Scheme 2.20. The chemical yields of the mesocyclic thiocrown ethers **2.30** and **2.31** are moderate. Due to the large sulfur atoms considerable ring-strain exists in these relatively small cycles. Extra ring strain is generated by the rigid bis-β-naphthyl unit, in which the naphthalene rings are almost perpendicular to each other. These effects significantly diminish the chemical yields in the ring closure reactions.
The cyclization reaction of **2.26** with 1,4,7-trithiaheptane to give **2.32** was not accompanied with racemization, as was demonstrated by HPLC analysis, on a chiral OT-column, of both racemic **2.32** and (*S*)-**2.32**, obtained by cyclization of enantiomerically pure **2.26**. We assumed that the

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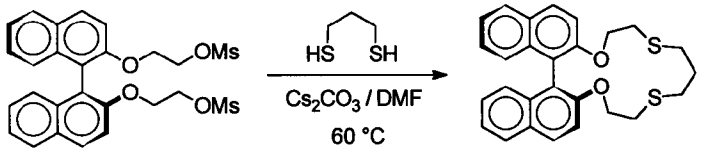
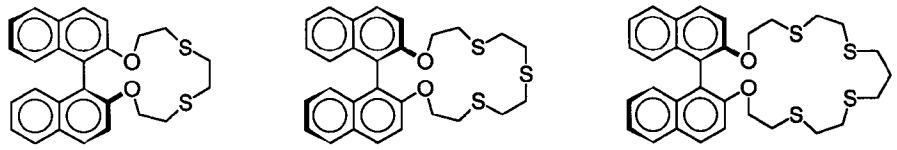
63 a) Alonso, M.E.; Aragona, H. *Org. Synth.* **1978**, *58*, 147. b) Kice, J.L. *J.Org.Chem.* **1963**, *28*, 957. c) Distler, H. *Angew.Chem.* **1967**, *79*, 520.
64 a) Speziale, A.J. *Org.Synth. Coll.Vol. IV* **1963**, 401. b) Reingold, I.D.; Schmidt, W.; Boekelheide, V. *J.Am.Chem.Soc.* **1979**, *101*, 2121.
65 Hojo, K.; Yoshino, H.; Mukaiyama, T. *Chem.Lett.* **1977**, 133.
66 Goor, G.; Antennis, M. *Phosphorus Sulfur* **1976**, *1*, 81.
67 a) Martin, D.J.; Grecco, C.C. *J.Org.Chem.* **1968**, *33*, 1275. b) Franzen, G.R.; Binsch, G. *J.Am.Chem.Soc.* **1973**, *95*, 175.
68 Eliel, E.L.; Rao, V.S.; Smith, S.; Hutchins, R.O. *J.Org.Chem.* **1975**, *40*, 524.

other ring closure reactions to thiocrown ethers were not accompanied with racemization either. The low yield in the cyclization step to thiocrown ethers **2.30** and **2.31** was independent of the leaving group in **2.26**. Ring closure with dibromide **2.34** (obtained from **2.26** by reaction with lithium bromide, see Scheme 2.21) gave **2.30** (31%) and **2.31** (33%) in essentially the same chemical yield as ring closure with bis-mesylate **2.26**.



2.26 **2.30**
(c.y. 30 %)

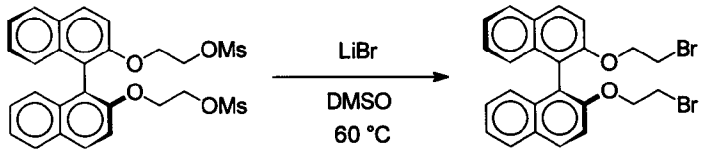
Analogously synthesized:



2.31 **2.32** **2.33**
(c.y. 32 %) (c.y. 58 %) (c.y. 54 %)

Scheme 2.20 *Thiocrown ethers derived from bis-mesylate 2.26*

Thiocrown ethers **2.30** - **2.33** were tested as ligands in several transition metal catalyzed asymmetric reactions (see Chapter 5). Unfortunately, the e.e.'s of the products in these reactions were low. This implies that the applied thiocrown ethers are either poor ligands for the transition metals used, or that they are good ligands, but are not able to transfer asymmetry to the substrates. In the latter case thiocrown ethers with other chiral backbones could be used as ligands to improve the e.e.'s.



2.26 **2.34**

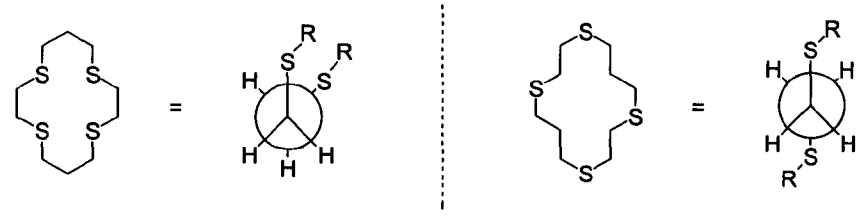
Scheme 2.21 *Synthesis of dibromide 2.34*

In order to examen the ligating properties of the thiocrown ethers we investigated the conformation of the heteroatoms in the thiocrown ligands.

2.10 *Conformation of thiocrown ether ligands*

The ligating properties of crown ether ligands depend on the number and the orientation of the heteroatoms in the free ligand. For oxocrown ethers a great deal of conformational analysis has been done by ^{13}C NMR studies and X-ray analysis.[69] Unfortunately, for thiocrown ethers ^{13}C NMR provides little insight into ligand conformation.[70] The chemical shifts for carbon atoms in thiocrown ethers are relatively insensitive to conformational changes. Furthermore, ^{13}C NMR studies on transition metal complexes of thiocrown ethers are often hindered by the fact that many transition metals are paramagnetic. Consequently, X-ray diffraction has played a crucial role in the study of thiocrown ether conformations. It should be noted, of course, that extrapolation of these solid state data to behavior in solution must be done with caution.

For optimal interaction between a crown ether ligand and a metal ion the orientation of the heteroatoms in the crown ether ring must be such that they can easily adopt a conformation in which they all point towards the cavity of the crown ether. In oxocrown ethers the O-C-C-O fragments in the molecule generally adopt a *gauche* conformation (torsional angle of 60°), whereas the C-O-C-C fragments adopt an *anti* conformation (torsional angle of 180°). When all the O-C-C-O fragments in an oxocrown ether are gauche, and all C-O-C-C fragments are anti, an overall conformation is obtained in which all O-atoms point towards the cavity of the crown ether (*endodentate* conformation). However, due to the large diameter of the sulfur atom, severe 1,4-repulsive interactions occur between the sulfur atoms in thiocrown ethers when the S-C-C-S fragments adopt a gauche conformation. These fragments therefore prefer an anti conformation. This generally results in gauche conformations for the C-S-C-C fragments. When all the S-C-C-S fragments in a thiocrown ether are anti, and all C-S-C-C fragments are gauche, an overall conformation is obtained in which all the sulfur atoms point away from the cavity of the crown ether (*exodentate* conformation).[71]



Scheme 2.22 *Exo- and endodentate conformations of 14S4*

Thiocrown ether ligands with exodentate sulfur atoms necessitate extensive conformational rearrangement before chelation of a metal ion can occur. This rearrangement costs energy. As a consequence, the greater the number of exodentate sulfur atoms, the weaker the tendency to chelate metal ions. When the loss of conformational energy is too great, thiocrown ether ligands will no longer chelate metal ions, but will form complexes in which one metal ion coordinates

69 Dale, J. *Isr.J.Chem.* **1980**, *20*, 3.
70 DeSimone, R.E.; Albright, M.J.; Kennedy, W.J.; Ochrymowycz, L.A. *Org.Magn.Res.* **1974**, *6*, 583.
71 DeSimone, R.E.; Glick, M.D. *J.Am.Chem.Soc.* **1976**, *98*, 762.

with two or more ligand molecules.[72] The thiocrown ether ligand then bridges two metal ions instead of chelating them.

X-ray analyses of the structures of 12S4,[73] 14S4[71] 15S5,[73] and other unfunctionalized[74] and functionalized[68, 72b,75] macrocyclic thioethers revealed that in practically every thiocrown ether *all* sulfur atoms are exodentate. Among the few exceptions known are 18S6[73,76] and 20S6[77] that have both endodentate and exodentate sulfur atoms. The small thiocrown ethers 6S3[78] and 9S3[79] are the only examples known in which *all* sulfur atoms are endodentate. Due to severe ring strain in 9S3 the S-C-C-S linkages cannot adopt an anti conformation, resulting in an all-endodentate thiocrown ether. As a result of the all-endodentate conformation of the sulfur atoms, 9S3 has extraordinary ligating abilities. The same reasoning is valid for 6S3, in which all sulfur atoms are linked by a methylene bridge. The two sulfur atoms of a thioacetal unit are forced to point to the same direction, resulting in an all-endodentate conformation for 6S3.

The question arose what the (solid state) conformation would be in the bis-β-naphthol derived thiocrown ethers **2.30 - 2.33**. We were interested in the effect of the rigid bis-β-naphthyl unit on the conformation of the heteroatoms in the crown. In order to determine the solid state conformation of the bis-β-naphthol derived thiocrown ethers single crystal X-ray analyses were carried out on **2.31** and **2.32**.

Suitable crystals of **2.31** were grown from chloroform by slow evaporation of the solvent. The compound crystallized in a cubic cell. From observation of systematic absences the space group was determined to be $P4_1$, Z = 4, with unit cell parameters: a = 11.6341(5) Å, b = 11.6341(6) Å, c = 15.8242(8) Å, V = 2141,8(2) Å^3; R = 0.050 and wR = 0.054. The structure was solved by direct methods. The remaining hydrogen atoms were revealed from one single Fourier difference synthesis based on all the non-hydrogen atoms. The crystal structure of **2.31** is depicted in Scheme 2.23 (top view) and Scheme 2.24 (side view). It can be seen that both sulfur atoms are exodentate in this solid state conformaition. From Table 2.5 it can be seen that the torsional angle between S1-C25-C26-S2 is 164.75°, which is an almost anti conformation. The torsional angle between O1-C21-C22-S1 is also almost anti (175.62°) whereas the torsional angle between O2-C26-C25-S2 is almost gauche (70.80°). The solid state conformation of **2.31** therefore is not preorganized for chelation of a metal ion. However, this does not imply that *endodentate*

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72 a) DeSimone, R.E.; Glick, M.D. *J.Am.Chem.Soc.* **1975**, *97*, 942. b) De Groot, B.; Loeb, S.J. *J.Chem.Soc.,Chem.Commun.* **1990**, 1755. c) Buter, J.; Kellogg, R.M.; Van Bolhuis, F. *J.Chem.Soc., Chem.Commun.* **1991**, 910. d) Willey, G.R.; Lakin, M.T.; Ravindran, M.; Alcock, N.W. *J.Chem.Soc.,Chem.Commun.* **1991**, 271. e) De Groot, B.; Jenkins, H.A.; Loeb, S.J. *Inorg.Chem.* **1992**, *31*, 203.

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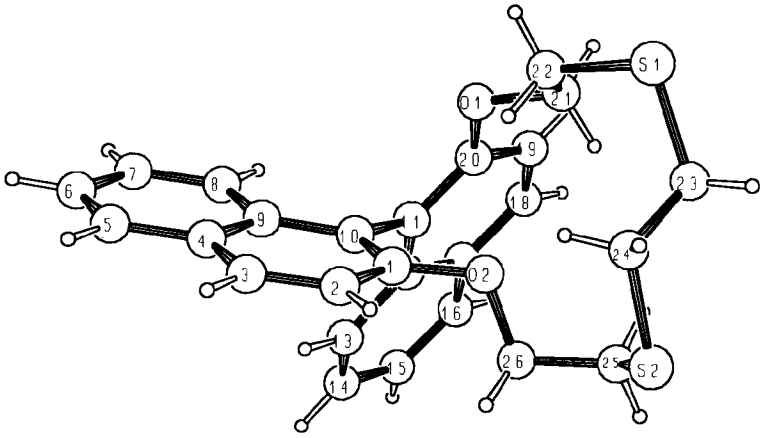
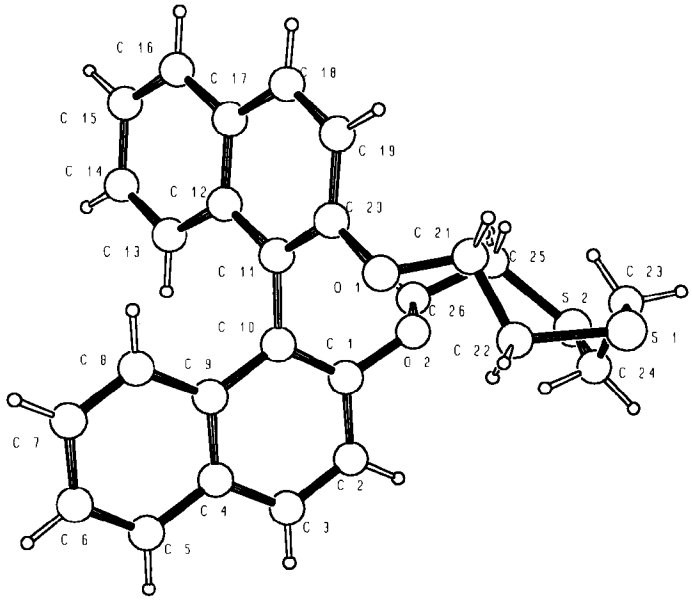
78 a) Edema, J.J.H.; Buter, J.; Van Bolhuis, F.; Meetsma, A.; Kellogg, R.M.; Kooijman, H.; Spek, A.L. *Inorg.Chim.Acta* **1993**, *207*, 263. b) Edema, J.J.H.; Hoogenraad, M.; Schoonbeek, F.S.; Kellogg, R.M.; Kooijman, H.; Spek, A.L. *Recl.Trav.Chim.Pays-Bas* **1993**, *112*, 370.

79 Glass, R.S.; Wilson, G.S.; Setzer, W.N. *J.Am.Chem.Soc.* **1980**, *102*, 5068.

complexation of metal ions is impossible.



Scheme 2.23 *Crystal structure of* ***2.31*** *(top view)*



Scheme 2.24 *Crystal structure of* ***2.31*** *(side view)*

Table 2.3 *Bond Distances of 2.31 (in Angstroms)*

atom 1	atom 2	Distance	atom 1	atom 2	Distance	atom 1	atom 2	Distance
S1	C22	1.809(4)	C4	C5	1.430(6)	C13	C14	1.370(6)
S1	C23	1.816(5)	C4	C9	1.429(6)	C14	C15	1.410(6)
S2	C24	1.823(5)	C5	C6	1.365(7)	C15	C16	1.362(6)
S2	C25	1.813(5)	C6	C7	1.414(6)	C16	C17	1.437(6)
O1	C20	1.371(5)	C7	C8	1.373(6)	C17	C18	1.415(6)
O1	C21	1.440(5)	C8	C9	1.416(6)	C18	C19	1.370(6)
O2	C1	1.382(5)	C9	C10	1.436(6)	C19	C20	1.409(6)
O2	C26	1.427(5)	C10	C11	1.487(5)	C21	C22	1.516(6)
C1	C2	1.417(6)	C11	C12	1.429(6)	C23	C24	1.529(6)
C1	C10	1.381(6)	C11	C20	1.382(6)	C25	C26	1.527(6)
C2	C3	1.367(6)	C12	C13	1.433(6)			
C3	C4	1.413(6)	C12	C17	1.417(6)			

Numbers in parentheses are estimated standard deviations in the least significant digits.

Table 2.4 *Selected Bond Angles of 2.31 (in degrees)*

Atom 1	Atom 2	Atom 3	Angle	Atom 1	Atom 2	Atom 3	Angle
C22	S1	C23	100.7(2)	O1	C21	C22	106.2(3)
C24	S2	C25	104.4(2)	S1	C22	C21	111.5(3)
C20	O1	C21	114.9(3)	S1	C23	C24	114.8(3)
C1	O2	C26	113.7(3)	S2	C24	C23	112.2(3)
O2	C1	C2	117.6(4)	S2	C25	C26	115.2(3)
O2	C1	C10	119.8(4)	O1	C20	C11	117.8(3)
C2	C1	C10	122.5(4)	O1	C20	C19	120.7(4)
O2	C26	C25	108.2(4)				

Numbers in parentheses are estimated standard deviations in the least significant digits.

Table 2.5 *Selected Torsional Angles of 2.31 (in degrees)*

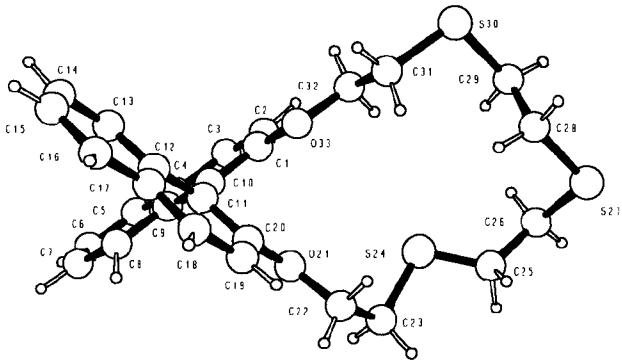
atom 1	atom 2	atom 3	atom 4	Angle	atom 1	atom 2	atom 3	atom 4	Angle
C23	S1	C22	C21	-66.56	S2	C25	C26	O2	70.80
C22	S1	C23	C24	-64.78	C1	C10	C11	C12	109.66
C25	S2	C24	C23	-65.44	C1	C10	C11	C20	-66.43
C24	S2	C25	C26	-72.54	C9	C10	C11	C12	-69.62
C21	O1	C20	C11	128.33	C9	C10	C11	C20	114.29
C21	O1	C20	C19	-53.44	C10	C11	C12	C13	3.45
C20	O1	C21	C22	-150.04	S1	C23	C24	S2	164.75
C26	O2	C1	C2	89.41	C12	C11	C20	O1	176.39
C26	O2	C1	C10	-95.22	O2	C1	C2	C3	175.97
C1	O2	C26	C25	-171.90	C10	C11	C20	O1	-7.41
O2	C1	C10	C9	-173.69	O1	C21	C22	S1	175.62
O2	C1	C10	C11	7.00					

Table 2.6 *Dihedral angles between planes of 2.31 (in degrees)*

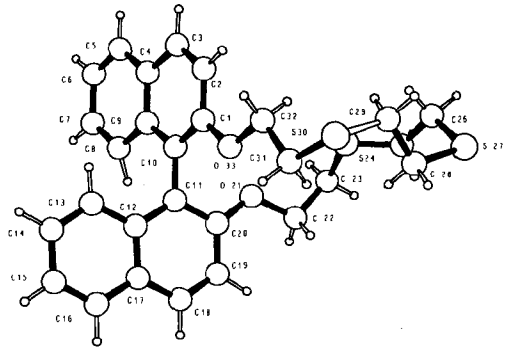
Plane 1: O1-O2-S1-S2
Plane 2: C1-C2-C3-C4-C5-C6-C7-C8-C9-C10
Plane 3: C11-C12-C13-C14-C15-C16-C17-C18-C19-C20

Plane No.	Plane No.	Dihedral angle
1	2	68.30 ± 0.07
1	3	77.58 ± 0.07
2	3	77.46 ± 0.08

From Table 2.6 it can be seen that the dihedral angles between both naphthalene rings is 68.30°. The dihedral angle between the plane of heteroatoms (O1-O2-S1-S2) and the planes of both naphthalene rings (C1 - C10 and C11 - C20) are 77.58° and 77.45°, respectively.



Scheme 2.25 *Crystal structure of 2.32 (top view)*



Scheme 2.26 *Crystal structure of 2.32 (side view)*

Suitable crystals of **2.32** were grown from THF by slow evaporation of the solvent. The compound crystallized in a triclinic space group P-1, Z = 2, with unit cell parameters: a = 10.694(1) Å, b = 11.085(1) Å, c = 12.578(2) Å, V = 1226.7(9) Å^3, α = 111.48(1)°, β = 114.22(2)°, λ = 93.32(2)°, R = 0.075 and wR = 0.084 (w = 1). The structure was solved by direct methods. The remaining hydrogen atoms were revealed from succeeding Fourier difference syntheses.

Bond C25-S24 is to some extent disordered. C25 and S24 have two sets of coordinates: C25/C25' and S24/S24', respectively, both with an occupancy ratio of approximately 0.5/0.5. This means that in solid state two conformations exist in about 1:1 ratio. In both conformations two sulfur atoms are exodentate (S27 and S30) and one sulfur (S24/S24') is endodentate. The endodentate sulfur atom can adopt two different gauche conformations. However, the overall conformations of **2.32** (with S24-C25) and **2.32'** (with S24'-C25') only show minor differences. The crystal structure of **2.32** is depicted in Scheme 2.25 (top view) and Scheme 2.26 (side view).

Table 2.7 *Selected Bond Distances of 2.32 (in Angstroms)*

atom 1	atom 2	Distance	atom 1	atom 2	Distane	atom 1	atom 2	Distance
S24	C25	1.53(2)	C22	C23	1.48(1)	C26	C25'	1.49(1)
S27	C26	1.827(7)	C25	C26	1.61(2)	C10	C11	1.497(6)
S27	C28	1.802(9)	C28	C29	1.53(1)	C25	C25'	0.86(2)
S30	C29	1.810(8)	S30	C31	1.814(4)	C25	S24'	1.78(1)
O21	C20	1.353(8)	O21	C22	1.432(8)	C23	S24'	1.778(7)
O33	C1	1.376(5)	O33	C32	1.426(4)	S24	C25'	1.77(2)
S24	S24'	0.984(6)	C22	C23	1.48(1)	C25	C26	1.61(2)
C31	C32	1.513(7)	C28	C29	1.53(1)	C1	C2	1.408(7)

Numbers in parentheses are estimated standard deviations in the least significant digits.

Table 2.8 *Selected Bond Angles of 2.32 (in degrees)*

Atom 1	Atom 2	Atom 3	Angle	Atom 1	Atom 2	Atom 3	Angle
C26	S27	C28	103.2(4)	O21	C20	C11	116.5(5)
C29	S30	C31	102.2(3)	O21	C20	C19	124.0(6)
C20	O21	C22	119.2(5)	O21	C22	C23	107.3(5)
C1	O33	C32	118.5(4)	S24	C25	C26	117.0(1)
O33	C1	C2	122.6(3)	S27	C26	C25	100.5(6)
O33	C1	C10	115.6(4)	S27	C28	C29	112.8(5)
S30	C29	C28	113.0(5)	S30	C31	C32	112.2(3)
O33	C32	C31	104.5(4)				

Numbers in parentheses are estimated standard deviations in the least significant digits.

Table 2.9 *Selected Torsion Angles of 2.32 (in degrees)*

atom 1	atom 2	atom 3	atom 4	Angle	atom 1	atom 2	atom 3	atom 4	Angle
C25	S24	C23	C22	118.40	C26	C25	S24'	C23	171.51
C23	S24	C25	C26	146.60	S27	C26	C25'	S24'	111.02
C28	S27	C26	C25	-64.77	C23	S24'	C25'	C26	-144.05
C28	S27	C26	C25'	-77.60	C26	S27	C28	C29	-65.12
C31	S30	C29	C28	-68.38	C29	S30	C31	C32	-75.95
C22	O21	C20	C11	173.72	C22	O21	C20	C19	-7.45
C20	O21	C22	C23	-175.28	C32	O33	C1	C2	-3.84
C32	O33	C1	C10	177.64	C1	O33	C32	C31	-177.84
O33	C1	C2	C3	-178.69	O33	C1	C10	C9	178.81
O33	C1	C10	C11	-1.94	C1	C10	C11	C12	105.34
C1	C10	C11	C20	-72.65	C18	C19	C20	O21	-179.02
O21	C22	C23	S24	70.46	O21	C22	C23	S24'	56.55
C22	C23	S24'	C25'	109.53	S24	C25	C26	S27	120.84
S27	C28	C29	S30	-179.61	S30	C31	C32	O33	-179.23

Table 2.10 *Dihedral angles between planes in 2.32 (in degrees)*

Plane 1: C1-C2-C3-C4-C5-C6-C7-C8-C9-C10
Plane 2: C11-C12-C13-C14-C15-C16-C17-C18-C19-C20
Plane 3: S24-S27-S30
Plane 4: S24'-S27-S30
Plane 5: O21-O33-S24-S27-S30
Plane 6: O21-O33-S24'-S27-S30

Plane No.	Plane No.	Angle	Plane No.	Plane No.	Angle
1	2	73.86	2	6	98.21
1	3	92.05	3	4	8.71
1	4	91.24	3	5	170.40
1	5	86.06	3	6	9.63
1	6	91.33	4	5	161.72
2	3	89.19	4	6	18.28
2	4	80.64	5	6	177.38
2	5	81.24			

Although thiocrown ethers generally have exodentate sulfur atoms, many transition metal complexes of thiocrown ethers are known in which the complexed ligand adopts an all-endodentate

geometry.[80] However, compared to azo- and oxocrown ethers, thiocrown ethers generally show only little macrocyclic effect (see Chapter 1). For example thiocrown ether 14S4 forms an endodentate complex with Ni(II) with a stability constant that is only a factor 180 higher than the stability constant of the Ni(II) complex of the corresponding open-chain tetrathioether analog.[81] This enhancement factor of about 200 is quite common for complexes of thiocrown ethers with transition metal ions,[82] and is wholly attributable to the more favorable entropy associated with the less flexible cyclic ligand compared to the open-chain ligand.[83] For azo- and oxocrown ethers the difference in stability constants between metal ion complexes of corresponding open-chain and cyclic polyethers (macrocyclic effect) is in the order of magnitude of 10^4-10^7 .[84]
Although thiocrown ethers **2.31** and **2.32** have exodentate sulfur atoms, they did form dark brown-red complexes with $Ni(BF_4)_2$ in acetonitrile. Unfortunately, we were not able to obtain suitable crystals for X-ray analysis. We therefore do not know whether the thiocrown ether ligands in these complexes chelate or bridge the Ni(II) ion.

2.11 *Propylene bridged thiocrown ethers*

Asymmetric catalysis with thiocrown ethers **2.30** - **2.33** as chiral ligands (Chapter 5) revealed that these compounds were poor ligands in transition metal catalysis. These poor ligating properties were probably caused by a high energy barrier between the unfavorable exodentate conformation of the sulfur atoms in the free ligands and the favorable endodentate conformation required for chelation. We wanted to diminish this energy barrier by diminishing the repulsive interactions between the sulfur atoms in the ring.
The easiest way to diminish repulsive sulfur-sulfur interactions is by elongating the distance between the sulfur atoms. We therefore synthesized thiocrown ethers with propylene bridges between the heteroatoms.
Alkylation of bis-β-naphthol with 3-chloro-1-propanol in DMF at 110 °C, analogous to the alkylation in Scheme 2.17, gave **2.36**. In order to force this alkylation to completeness it was performed with 4 equivalents of base and 4 equivalents of 3-chloro-1-propanol. However, under these conditions not all the bis-β-naphthol was converted into **2.36**, but a considerable amount of mono-alkylated product **2.35** was obtained (see Scheme 2.27). Even when the reaction mixture was stirred for several days at 110 °C considerable amounts of mono-alkylated **2.35** were still present. Furthermore, the dimer of 3-chloro-1-propanol was formed as a byproduct. Obviously, the reaction of 3-chloro-1-propanol with itself, upon formation of dimer **2.37**, is competitive with the alkylation of bis-β-naphthol. A large excess of 3-chloro-1-propanol is probably required to force this alkylation to completeness. However, we did not optimize this reaction, as the components of the reaction mixture could be separated quite easily. Most of dimer **2.37** was removed by bulb to bulb distillation (0.1 mm Hg, 225°C). The residue of distillation was chromatographed to give **2.35** in 21% yield and **2.36** in 59% yield.
Competitive formation of **2.37** could be prevented by alkylating bis-β-naphthol with tetrahydro-

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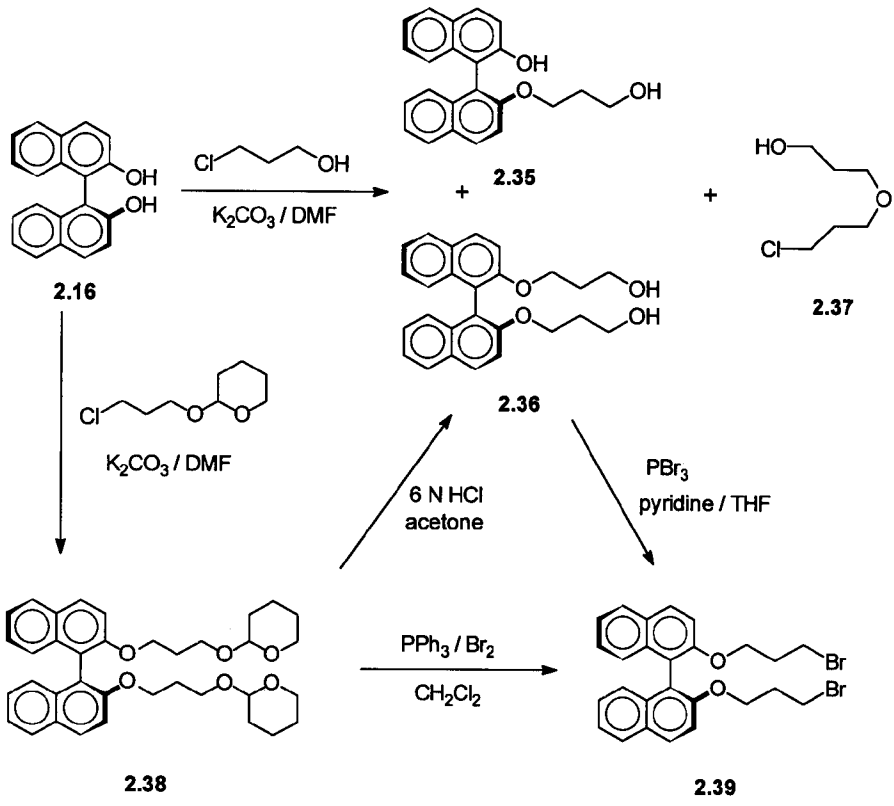


Scheme 2.27 *Synthesis of bis-bromide 2.39*

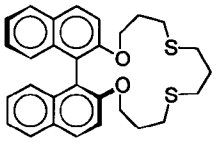
pyranyl (THP) protected 3-chloro-1-propanol. In this case we were able to force the alkylation to completion. Bis-THP ether **2.38** was obtained as a mixture of diastereomers in 89% chemical yield. Crude **2.38** was deprotected by hydrolysis with 6 N HCl to give **2.36** in 95% chemical yield. Subsequent reaction with PBr_3 and pyridine gave **2.39** in 19% chemical yield. The bromination of **2.36** was accompanied by formation of considerable amounts of elimination products. We therefore searched for another route to **2.39**.

Since the alkylation of bis-β-naphthol went better with THP-protected 3-chloro-1-propanol than with unprotected 3-chloro-1-propanol we wanted to convert **2.38** to **2.39** directly. In the literature several methods are known for direct functionalization of THP ethers.[85] THP ethers can be converted to bromides by reaction with $LiBr/BF_3{\cdot}Et_2O$ or $LiBr/ClSiMe_3$. However, reaction of **2.38** with these reagents led to formation of complex reaction mixtures. When **2.38** was allowed to react with triphenylphosphine and bromine, analogous to the method described by Schwarz et al.[86], **2.39** was obtained in 73% chemical yield. A disadvantage of this reaction is the excess (5

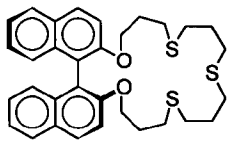
85 a) Vankar, Y.D.; Shah, K. *Tetrahedron Lett.* **1991**, *32*, 1081. b) Sato, T.; Tada, T.; Otera, J.; Nozaki, H. *Tetrahedron Lett.* **1989**, *30*, 1665.

86 Schwarz, M.; Oliver, J.E.; Sonnet, P.E. *J.Org.Chem.* **1975**, *40*, 2410.

equivalents) of triphenylphosphine that has to be used, resulting in a huge amount of triphenylphosphine oxide as byproduct. This byproduct was removed by crystallization from toluene/n-octane. After thorough washing of the crystals (triphenylphosphine oxide) with n-hexane, the filtrate was purified by chromatography to give pure **2.39**.
Dibromide **2.39** was cyclized with 1,3-propanedithiol and with 1,5,9-trithianonane (**2.40**, not depicted), analogously to Scheme 2.20, to give thiocrown ethers **2.41** and **2.42**, respectively.



2.41
(c.y. 61%)



2.42
(c.y. 47%)

Scheme 2.28 *Propylene bridged thiocrown ethers*

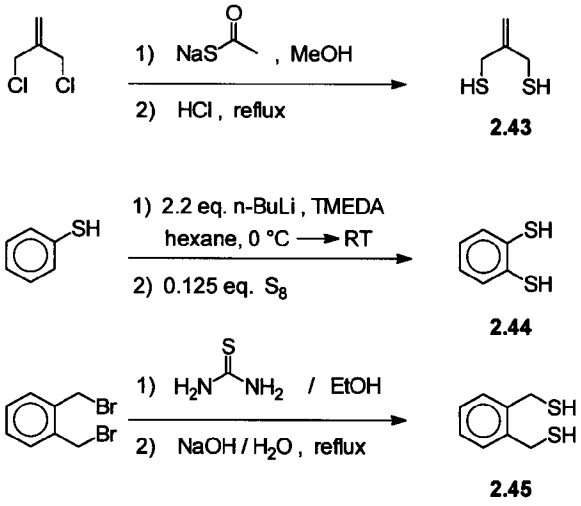
Thiocrown ethers **2.41** and **2.42** were tested as ligands in several transition metal catalyzed asymmetric syntheses (see Chapter 5). However, just as with the ethylene bridged thiocrown ethers **2.30** - **2.33** (Chapter 2.9), the obtained e.e.'s were low. It turned out that elongation of the sulfur-sulfur distances in the thiocrown ether molecule did not have a significant effect on its abilities as chiral ligand in transition metal catalyzed reactions.
Two effects play a role on the ability as chiral ligand of the propylene bridged thiocrown ethers. The first effect is that the propylene bridged thiocrown ethers have a diminished sulfur-sulfur repulsion and an enhanced flexibility as compared to the ethylene bridged thiocrown ethers. This will probably result in a somewhat better chelation of metal ions by the propylene bridged thiocrown ethers. A second, unfavorable effect of propylene bridges instead of ethylene bridges is the increased cavity size. A metal ion chelated by a propylene bridged thiocrown ether will be farther away from the chiral bis-β-naphthol unit than it would be when it was chelated by a corresponding ethylene bridged thiocrown ether. When applied in asymmetric catalysis, the substrate, coordinated to the metal center, will then 'feel' less the chiral influence of the ligand. A larger cavity size might therefore result in lower asymmetric induction.
Although the ring size of the thiocrown ether will have an influence on the effectiveness as a chiral ligand, the most important condition for being a good ligand will be the capacity of chelating metal ions. We therefore searched for other methods for improving the chelating capability of thiocrown ethers.

2.12 *Thiocrown ethers with incorporated rigid subunits*

In the previous chapter we have seen that elongation of the distance between the sulfur atoms in the bis-β-naphthol derived thiocrown ethers did not improve the ability to induce asymmetry in transition metal catalyzed reactions: both the ethylene- and the propylene bridged thiocrown ethers give low e.e.'s as ligands in a whole variety of reactions (see Chapter 5). We assume that both types of ligands have modest chelating capacities. A route to improve the chelating capacity of thiocrown ethers is to modify the thiocrown ether ring in such a way that the free ligand is forced to adopt a more endodentate conformation. This can be achieved by incorporation of rigid

subunits in the thiocrown ether, like thioacetals[78], 1,2-dicyano-1,2-dithioethene[87] or tetrathiofulvalene[88].

The rigidity was introduced by cyclization of ethylene bridged **2.26** or propylene bridged **2.39** with (semi)rigid dithiols. The (semi)rigid dithiols **2.43**[89], **2.44**[90] and **2.45**[91] were synthesized according to literature procedures (Scheme 2.29).



Scheme 2.29 *Synthesis of (semi)rigid dithiols*

The thiocrown ethers **2.46** - **2.49**, derived from dithiols **2.43** - **2.45**, are depicted in Scheme 2.30. The chemical yields of the ring closure step are given in parentheses.

The chelating capacity of thiocrown ethers can also be improved by incorporation of subunits that cause steric hindrance when they adopt an exodentate conformation. Recently, Desper and Gellman described the synthesis of thiocrown ethers containing gem-dimethyl subunits.[92] The gem-dimethyl groups dramatically alter the backbone conformation of the free thiocrown ether ligands. The C-S-C-C(H_2) fragments in 14S4 and **2.50** adopt a gauche conformation whereas the corresponding C-S-C-C(Me_2) fragments in **2.50** and **2.51** adopt an anti conformation. Furthermore in **2.50** one of the S-C-C-S bonds is gauche, whereas in **2.51** both S-C-C-S bonds are gauche. This

87 a) Holdt, H.-J. *Pure Appl.Chem.* **1993**, *65*, 477. b) Märkl, G.; Vybiral, R. *Tetrahedron Lett.***1989**, *30*, 2903.

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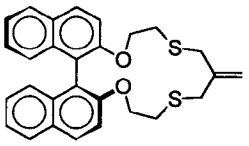
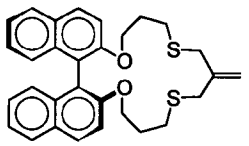
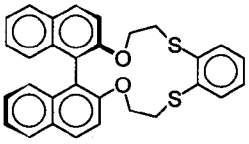
92 a) Desper, J.M.; Gellman, S.H. *J.Am.Chem.Soc.* **1990**, *112*, 6732. b) Desper, J.M.; Gellman, S.H. *J.Am.Chem.Soc.* **1991**, *113*, 704. c) Desper, J.M.; Gellman, S.H.; Wolf, R.E.; Cooper, S.R. *J.Am.Chem.Soc.* **1991**, *113*, 8663. d) Nazarenko, A.Y.; Izatt, R.M.; Lamb, J.D.; Desper, J.M.; Matysik, B.E.; Gellman, S.H. *Inorg.Chem.* **1992**, *31*, 3990. e) Desper, J.M.; Vyvyan, J.R.; Mayer, M.J.; Ochrymowycz, L.A.; Gellman, S.H. *Inorg.Chem.* **1993**, *32*, 381.



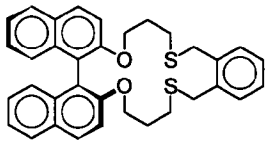
2.46
(c.y. 20%)



2.47
(c.y. 68%)



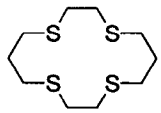
2.48
(c.y. 72%)



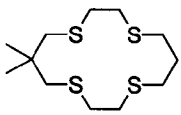
2.49
(c.y. 61%)

Scheme 2.30 *Thiocrown ethers with (semi)rigid subunits*

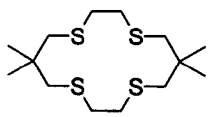
results in a solid state conformation of **2.51** in which all four sulfur atoms point one lone pair to the cavity of the crown. Due to these peripheral modifications in the backbone of the crown ether the free ligand has a more preorganized conformation for chelation of a metal ion. This results in enhanced affinity for metal ions in the order 14S4 < **2.50** < **2.51** as was demonstrated by competition experiments. Equimolar amounts of 14S4 and either **2.50** or **2.51** and one equivalent of a Ni(II) salt were dissolved in nitromethane-d_3 and after equilibrating for several days at room temperature the distribution of complexed and uncomplexed ligands was determined by ^{1}H NMR. The affinity of **2.50** and **2.51** for Ni(II) was 7 and 50 times larger, respectively, than that of 14S4. The affinity for Cu(II) of **2.50** and **2.51** was 5 and 23 times larger, respectively, than that of 14S4 as was determined by UV spectroscopy.[92b]



14S4



2.50

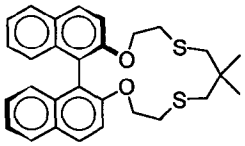


2.51

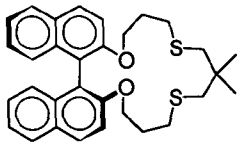
Scheme 2.31 *Gem-dimethyl derivatives of 14S4*

The beneficial effect of the gem-dimethyl group on the affinity for transition metal ions inspired us to apply this subunit to our system. We allowed **2.26** and **2.39** to react with 2,2-dimethyl-1,3-propanedithiol[68, 72] (**2.52**) to give **2.53** (30% chemical yield) and **2.54** (24% chemical yield), which are the gem-dimethyl analogs of **2.30** and **2.41**, respectively.
Thiocrown ether **2.53** turned out to be a good host-molecule for ethanol. In attempt to purify **2.53** by recrystallization from ethanol a stable host-guest complex was obtained. ^{1}H and ^{13}C NMR spectra showed signals for the complexed host molecule and for complexed ethanol. The ethanol in the complex could not be exchanged for another solvent molecule by heating the complex in

$CHCl_3$, CH_2Cl_2 or CCl_4. When the complex was eluted on a silica gel column with toluene/n-hexane, uncomplexed material was obtained.



2.53



2.54

Scheme 2.32 *Gem-dimethyl derivatives of bis-β-naphthol derived thiocrown ethers*

Attempts to determine the relative affinity of **2.53** and **2.54** for transition metal ions compared to the corresponding ligands lacking the gem-dimethyl group (**2.30** and **2.41**), by means of ^1H NMR, analogous to Desper and Gellman[92], failed, since no separate signals were observed for the complexed and uncomplexed ligands containing a gem-dimethyl unit.
Compounds **2.53** and **2.54** were applied as ligands in asymmetric catalysis (see Chapter 5). The asymmetric inductions obtained with these ligands were higher than with the corresponding thiocrown ethers lacking the gem-dimethyl subunit. However, the presence of a gem-dimethyl subunit in the ligand turned out to have only a minor beneficial effect on the asymmetric induction.

2.13 *Summary and conclusions*

Several thiocrown ethers, derived from bis-β-naphthol, were synthesized. The synthesis, starting with optically pure bis-β-naphthol, was performed without racemization when K_2CO_3 in DMF were applied in the alkylation step. The chemical yields of the ring closure reactions upon formation of the thiocrown ethers were moderate to good. The solid state conformations of **2.31** and **2.32** were determined. In **2.31** all sulfur atoms were exodentate, whereas in **2.32** two sulfur atoms were exodentate and one sulfur atom was endodentate. For optimal ligating properties all sulfur atoms in a thiocrown ether ligand should be endodentate. In order to facilitate the endodentate conformation compared to the exodentate conformation, propylene bridges between the sulfur atoms and (semi)rigid subunits were introduced in the thiocrown ethers. The consequences of these modifications on the effectiveness of the chiral thiocrown ethers as ligands in asymmetric catalysis will be described in Chapter 5.

2.14 *Experimental section*

General remarks: All reactions were performed in a nitrogen atmosphere, unless otherwise stated. Melting points (uncorrected) were determined on a Mettler FP-2 melting point apparatus, equipped with a Mettler FP-21 microscope, or on a Thermopan Reichert Austria apparatus. Optical rotations were measured at room temperature (20°C) on a Perkin-Elmer 241 polarimeter at the Sodium D line (589 nm) and at the Mercury lines (578 nm, 546 nm, 436 nm, 365 nm). ^1H NMR spectra were recorded on a Hitachi Perkin Elmer R-24B High Resolution NMR spectrometer (60 MHz), on a JEOL JNM-PMX60 si NMR spectrometer (60 MHz), on a Varian Gemini-200 NMR spectrometer (200 MHz) or on a Varian VXR-300 NMR spectrometer (300 MHz). Chemical shifts are denoted in δ-units (ppm) relative to tetramethylsilane (TMS) as an internal standard (δ = 0 ppm) or relative to the solvent and converted to the TMS scale using δ ($CHCl_3$)

= 7.26 ppm. ^{13}C NMR spectra were recorded on a Varian Gemini-200 NMR spectrometer (at 50.3 MHz) or on a Varian VXR-300 NMR spectrometer (at 75.4 MHz). Chemical shifts are denoted in δ-units (ppm) relative to the solvent and converted to the TMS scale using δ ($CHCl_3$) = 76.91 ppm. The splitting patterns are designated as: s (singlet), d (doublet), dd (double doublet), t (triplet), q (quartet), m (multiplet) and br (broad). Infrared spectra were recorded on a Perkin-Elmer 257 spectrophotometer. Mass spectra were recorded on an AEI-MS-902 mass spectrometer by Mr. A. Kiewiet. Elemental analyses were performed in the Microanalytical Department of this laboratory by Mr. H. Draayer, J. Ebels, J. Hommes, and J.E. Vos. X-ray analyses were performed by Mr. F. van Bolhuis with Mo K_α radiation (λ = 0.71073 Å) on a Nonius CAD4F computer controlled kappa axis diffractometer equipped with a graphite crystal, incident beam monochromator and interfaced to a VAX-730. All solvents and reagents were purified and dried, following standard procedures.[93] Reagents were purchased from Janssen Chimica, Aldrich Chemical Company and Fluka. Bis-β-naphthol was purchased from Syncom BV. 1,4,7-Trithiaheptane was purchased from Aldrich Chemical Company. Compounds **2.44**[90] and **2.52**[68,89] were prepared according to literature procedures. In some substitution reactions 4-N,N-dimethylaminopyridine (DMAP) was added as hypernucleophilic catalyst.[61]

2'-Ethoxy-1,1'-binaphthyl-2-ol (2.18)[94] and ***2,2'-diethoxy-1,1'-binaphthyl (2.19)***[95]

The extent of racemization during the ethylation of (*R*)-**2.16**, and the ratio of mono- and bisalkylation were studied under a variety of conditions. Compounds **2.18**[94] and **2.19**[95] have been prepared previously.

With KO^{t}Bu/THF (procedure A): A solution of (*R*)-**2.16** (286 mg, 1.00 mmol), KO^{t}Bu (0.34 g, 3.0 mmol) and ethyl bromide (0.30 mL, 4.0 mmol) in THF (15 mL) was refluxed for 24 h. The reaction mixture was cooled to rt, filtered and concentrated under reduced pressure to give a white solid (330 mg). The crude product was filtered over a short silica gel column (CH_2Cl_2) to give **2.19** (94%) with no trace of **2.18**: mp 135.1 - 136.2 °C; ^1H NMR ($CDCl_3$, 200 MHz): δ 1.10 (t, J = 7.0 Hz, 6 H), 4.09 (q, J = 7.0 Hz, 4 H), 7.17 - 7.49 (m, 8 H), 7.90 (d, J = 7.9 Hz, 2 H), 7.98 (d, J = 9.0 Hz, 2 H); ^{13}C NMR ($CDCl_3$, 50.3 MHz): δ 15.0 (q), 65.2 (t), 115.9 (d), 120.7 (s), 123.4 (d), 125.5 (d), 126.1 (d), 127.8 (d), 129.1 (d), 129.3 (s), 134.2 (s), 154.3 (s); e.e. 98.6%, as determined by HPLC[96].

With NaH/DMF (procedure B): A solution of (*R*)-**2.16** (286 mg, 1.00 mmol) and NaH (a 55% suspension in oil; 131 mg, 3.00 mmol) in DMF (15 mL) was stirred at rt for 15 min. Ethyl bromide (0.50 mL, 7.0 mmol) was added and the reaction mixture was stirred at 110°C for 24 h. The mixture was cooled to rt, filtered and concentrated under reduced pressure to give a yellowish brown oil (1028 mg). The crude product was dissolved in CH_2Cl_2 (50 mL) and washed with 1 N HCl (50 mL). The CH_2Cl_2 layer was separated and the water layer was washed with CH_2Cl_2 (2 x 50 mL). The combined organic layers were dried ($MgSO_4$) and concentrated under reduced pressure to give yellow oil (410 mg). The crude product was filtered over a short silica gel column (CH_2Cl_2) to give a mixture of **2.18** (16%) and **2.19** (84%): ^1H NMR ($CDCl_3$, 200 MHz): δ 1.08 (t, J = 7.0 Hz; CH_3 **2.19**), 1.12 (t, J = 7.0 Hz, CH_3 **2.18**), 4.07 (q, J = 7.0 Hz, CH_2 **2.18** and **2.19**), 5.01 (s, OH, **2.18**), 7.15 - 7.47 (m, Ar-H, **2.18** and **2.19**), 7.88 (d, J = 8.0 Hz, Ar-H, **2.18** and **2.19**), 7.97 (d, J = 9.0 Hz, Ar-H, **2.19**), 8.02 (d, J = 9.2 Hz, Ar-H, **2.18**); e.e. of **2.19**: 98.3%, as determined by HPLC[96].

With K_2CO_3/acetone: (*R*)-**2.16** (286 mg, 1.00 mmol), K_2CO_3 (0.41 g, 3.0 mmol) and ethyl

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93 Vogel's "*Textbook of Practical Organic Chemistry*", Fourth Ed. Longman, London, **1978**.

94 Pirkle, W.H.; Schreiner, J.L. *J.Org.Chem.* **1981**, *46*, 4988.

95 Zinke, A.; Dengg, R. *Monatsh.Chem.* **1922**, *43*, 127.

96 A water cooled 250 x 4.6 mm (+)-poly(triphenylmethylmethacrylate) column (DAICEL OT$^+$) was used, with *n*-hexane/*i*-propanol 100:1 as eluent (flow 0.5 mL/min); retention times: (*S*)-**2.19**: 34.76 min; (*R*)-**2.19**: 42.95 min.
a) Okamoto, Y.; Honda, S.; Okamoto, I.; Yuki, K.; Murata, S.; Noyori, R.; Takaya, H. *J.Am.Chem.Soc.* **1981**, *103*, 6971. b) Okamoto, Y.; Hatada, K. *J.Liq.Chromatogr.* **1986**, *9*, 369.

bromide (0.30 mL, 4.0 mmol) were dissolved in acetone (15 mL) and refluxed for 24 h. Workup according to procedure A afforded a mixture of **2.18** (5%) and **2.19** (93%). ^1H and ^{13}C NMR were in accordance with the expected structure. E.e. of **2.19**: 99.6%, as determined by HPLC[96].

With K_2CO_3/acetonitrile: (*R*)-**2.16** (286 mg, 1.00 mmol), K_2CO_3 (0.41 g, 3.0 mmol) and ethyl bromide (0.30 mL, 4.0 mmol) were dissolved in acetonitrile (15 mL) and refluxed for 24 h. Workup according to procedure A afforded **2.19** (100%). E.e. of **2.19**: 99.0%, as determined by HPLC[96].

With K_2CO_3/DMF, reflux: (*R*)-**2.16** (286 mg, 1.00 mmol), K_2CO_3 (0.41 g, 3.0 mmol) and ethyl bromide (0.30 mL, 4.0 mmol) were dissolved in DMF (15 mL) and refluxed for 24 h. Workup according to procedure A afforded **2.19** (100%). E.e. of **2.19**: 98.5%, as determined by HPLC[96].

With K_2CO_3/DMF, 110°C: (*R*)-**2.16** (286 mg, 1.00 mmol), K_2CO_3 (0.41 g, 3.0 mmol) and ethyl bromide (0.30 mL, 4.0 mmol) were dissolved in DMF (15 mL) and stirred at 110°C for 24 h. Workup according to procedure A afforded **2.19** (100%). E.e. of **2.19**: 99.6%, as determined by HPLC[96].

With K_2CO_3/DMF, 70°C: (*R*)-**2.16** (286 mg, 1.00 mmol), K_2CO_3 (0.41 g, 3.0 mmol) and ethyl bromide (0.30 mL, 4.0 mmol) were dissolved in DMF (15 mL) and stirred at 70°C for 24 h. Workup according to procedure A afforded a mixture of **2.18** (8%) and **2.19** (92%). E.e. of **2.19**: 99.6%, as determined by HPLC[96].

2',3'-Dihydro-spiro[naphthalene-1(2H),1'-[1H]naphtho[2,1-b]pyran]-2-one (2.24)[34a]

(±)-Bis-β-naphthol (0.86 g, 3.0 mmol), 1-chloro-2-tosyloxyethane[97] (1.41 g, 6.0 mmol) and K_2CO_3 (0.92 g, 6.7 mmol) were dissolved in DMF (100 mL) and refluxed for 17 h. The reaction mixture was concentrated under reduced pressure, was taken up in Et_2O (150 mL) and washed with water (100 mL), 2N NaOH (2 x 100 mL) and brine (100 mL). The organic layer was dried (Na_2SO_4) and concentrated under reduced pressure to give a yellow solid (0.99 g). The crude product was purified by column chromatography (silica gel, Et_2O/n-pentane 1:1) to give a yellow solid (0.41 g), that was recrystalized from toluene to give **2.24** (28 %) as white crystals: mp 199-201°C (lit.[34a] 198-200°C); ^1H NMR ($CDCl_3$, 300 MHz): δ 2.04 - 2.14 (m, 1 H), 2.31 - 2.40 (m, 1 H), 4.08 - 4.16 (m, 1 H), 4.23 - 4.31 (m, 1 H), 6.31 (d, J = 9.9 Hz, 1 H), 6.51 (d, J = 8.4 Hz, 1 H), 6.78 (d, J = 8.1 Hz, 1 H), 6.98 - 7.18 (m, 5 H), 7.36 (d, J = 7.3 Hz, 1 H), 7.55 - 7.68 (m, 3 H); ^{13}C NMR ($CDCl_3$, 75.4 MHz): δ 37.9 (t), 53.0 (s), 59.9 (t), 114.3 (s), 118.8 (d), 122.7 (d), 123.7 (d), 124.0 (d), 126.0 (d), 126.8 (d), 127.5 (d), 128.3 (s), 128.3 (d), 129.5 (d), 129.6 (d), 129.9 (s), 130.0 (d), 131.3 (s), 144.4 (d), 147.5 (s), 155.0 (s), the ^{13}C-signal for C=O was not seen; IR (KBr): 1660 cm^{-1} (C=O); HRMS *m/e* (M^+) calcd 312.115, obsd 312.116.

(R)-(-)-2,2'-Bis(2-hydroxyethoxy)-1,1'-binaphthyl (2.25)

The literature procedure for preparation of the (*S*)-enantiomer[34a] was improved and applied for preparation of both (*R*)- and (*S*)-**2.25**: (*R*)-(+)-bis-β-naphthol (8.62 g, 30.1 mmol), 2-chloroethanol (8.0 mL, 119 mmol) and K_2CO_3 (16.6 g, 120 mmol) were dissolved in DMF (250 mL) and stirred at 110°C for 17 h. The reaction mixture was filtrated and concentrated under reduced pressure. The residue was taken up in CH_2Cl_2 (150 mL) and washed with water (2 x 100 mL) and 2 N NaOH (100 mL). The organic layer was dried ($MgSO_4$) and concentrated under reduced pressure to give a pale yellow oil (12.15 g). The crude product was purified by column chromatography (silica gel, Et_2O) giving **2.25** (77%) as a white foam: mp 130-134°C; $[\alpha]_{578}$ = - 26.4 (c = 0.762, THF), $[\alpha]_{546}$ = - 26.6; $[\alpha]_{436}$ = + 14.0; $[\alpha]_{365}$ = + 543.8; ^1H NMR ($CDCl_3$, 200 MHz): δ 2.42 (s, br, 2 H), 3.45 - 3.70 (m, br, 4 H), 3.98 - 4.07 (m, 2 H), 4.18 - 4.28 (m, 2 H), 7.13 - 7.48 (m, 8 H), 7.91 (d, J = 7.3 Hz, 2 H), 8.00 (d, J = 9.0 Hz, 2 H); ^{13}C NMR ($CDCl_3$, 50.3 MHz): δ 61.2 (t), 71.7 (d), 115.9 (d), 120.3 (s), 124.1 (d), 125.2 (d), 126.7 (d), 128.2 (d), 129.6 (s), 129.8 (d), 133.8 (s), 153.5 (s); HRMS *m/e* (M^+) calcd 374.152, obsd 374.152.

(S)-(+)-2.25[34a] By the same procedure (*S*)-**2.25** (71%) was obtained: mp 131-134°C; $[\alpha]_{578}$ = +

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25.1 (c = 0.958, THF), $[\alpha]_{546}$ = + 25.4 (lit.[34a] $[\alpha]_{546}$ = + 23.2 (c = 1.05, THF)); $[\alpha]_{436}$ = - 13.4; $[\alpha]_{365}$ = + 522.6.

(R,S)-2.25 by hydrolysis of 2.27
A solution of **2.27** (1.95 g, 3.60 mmol) in acetone (50 mL) and 2 N HCl (15 mL) was was refluxed for 4 h. Water (150 mL) was added and the reaction mixture was extracted with CH_2Cl_2 (3 x 100 mL). The combined organic layers were washed with brine (150 mL), dried ($MgSO_4$) and concentrated under reduced pressure to give a yellow oily solid (1.28 g). The crude product was suspended in Et_2O (25 mL) and stirred in an ultrasound bath to give **2.25** (44 %) as a white powder: mp 110.3 - 110.6 °C; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.83 (s, 6 H), 3.93 - 4.11 (m, 8 H), 6.90 - 7.25 (m, 8 H), 7.66 - 7.71 (m, 2 H), 7.77 - 7.82 (m, 2 H); ^{13}C NMR ($CDCl_3$, 75.4 MHz): δ 35.9 (q), 67.0 (t), 68.7 (t), 114.8 (d), 119.7 (s), 124.1 (d), 125.0 (d), 126.7 (d), 127.8 (d), 129.3 (s), 129.6 (d), 133.7 (s), 153.2 (s).

(R)-(-)-2,2'-Bis(2-mesyloxyethoxy)-1,1'-binaphthyl (2.26)
To a solution of (*R*)-**2.25** (1.87 g, 5.0 mmol), triethylamine (1.5 mL, 11 mmol) and DMAP (20 mg, 0.16 mmol) in CH_2Cl_2 (75 mL) was dropwise added methanesulfonyl chloride (0.85 mL, 11.0 mmol) at 0°C. The reaction mixture was stirred at room temperature for 17 h and subsequently washed with water (2 x 50 mL). The organic layer was dried ($MgSO_4$) and concentrated under reduced pressure to give a viscous, slightly yellow oil (2.80 g). The crude product was crystallized from toluene/n-hexane to give **2.26** (95 %) as white crystals: mp 143-144°C; $[\alpha]_{578}$ = - 30.5 (c = 0.650, THF); $[\alpha]_{546}$ = - 32.8; $[\alpha]_{436}$ = - 24.3; $[\alpha]_{365}$ = + 237; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.83 (s, 6 H), 3.93 - 4.11 (m, 8 H), 6.90 - 7.25 (m, 8 H), 7.66 - 7.71 (m, 2 H), 7.77 - 7.82 (m, 2 H); ^{13}C NMR ($CDCl_3$, 75.4 MHz): δ 35.9 (q), 67.0 (t), 68.7 (t), 114.8 (d), 119.7 (s), 124.1 (d), 125.0 (d), 126.7 (d), 127.8 (d), 129.3 (s), 129.6 (d), 133.7 (s), 153.2 (s); HRMS *m/e* (M^+) calcd 530.107, obsd 530.106; Anal. Calcd (found) for $C_{26}H_{26}O_8S_2$: C, 58.85 (58.67); H, 4.94 (5.03); S, 12.09 (11.98).
(S)-(+)-2.26 By the same procedure (*S*)-**2.26** (92%) was obtained: mp 142-143 °C; $[\alpha]_{578}$ = + 30.4 (c = 0.834, THF); $[\alpha]_{546}$ = + 32.6; $[\alpha]_{436}$ = + 24.4; $[\alpha]_{365}$ = - 234.

2,2'-Bis(2-(pyranyl-2-oxy)-ethoxy)-1,1'-binaphthyl (2.27)
(±)-Bis-β-naphthol (2.86 g, 10.0 mmol), 2-(2-chloroethoxy)-pyran[98] (3.30 g, 20.0 mmol) and K_2CO_3 (3.05 g, 22 mmol) was dissolved in DMF (150 mL) and refluxed for 17 h. The reaction mixture was concentrated under reduced pressure, the residue was taken up in Et_2O (200 mL) and washed with water (2 x 150 mL), 2N NaOH (2 x 100 mL) and brine (100 mL). The organic layer was dried (Na_2SO_4) and concentrated under reduced pressure to give a yellow oil (5.26 g). The crude product was purified by column chromatography (silica gel, Et_2O/Et_3N 250 : 1) to give **2.27** (89 %) as pale yellow oil: ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.12 - 1.57 (m, 12 H), 3.02 - 3.14 (m, 2 H), 3.26 - 3.48 (m, 4 H), 3.58 - 3.69 (m, 2 H), 4.04 - 4.13 (m, 5 H), 4.17 - 4.20 (m, 1 H), 7.10 - 7.27 (m, 6 H), 7.38 - 7.41 (m, 2 H), 7.79 (d, J = 8.1 Hz, 2 H), 7.87 (dd, J_1 = 8.8 Hz, J_2 = 2.6 Hz, 2 H); ^{13}C NMR ($CDCl_3$, 75.4 MHz): δ 18.7 (t), 18.7 (t), 25.0 (t), 29.8 (t), 30.0 (t), 61.0 (t), 61.2 (t), 65.2 (t), 65.3 (t), 68.8 (t), 68.9 (t), 97.9 (d), 98.2 (d), 115.2 (d), 115.3 (d), 120.1 (s), 120.2 (s), 123.2 (d), 125.1 (d), 125.8 (d), 127.4 (d), 128.7 (d), 128.8 (d), 129.0 (s), 133.8 (s), 154.0 (s); HRMS *m/e* (M^+) calcd 542.267, obsd 542.268.

1,9-Dihydroxy-3,7-dithianonane (2.28)[5,13]
This compound was prepared according to a procedure described in literature[5,13], from 1,3-propanedithiol (50 mL, 0.50 mol) and 2-chloroethanol (100 mL, 1.49 mol) giving **2.28** (75%) as a pale yellow oil: bp 182 °C (0.35 mm Hg) (lit.[5] 179 - 181.5 °C, 0.5 mm Hg); ^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.80 (quintet, J = 7.1 Hz, 2 H), 2.58 (t, J = 7.1 Hz, 4 H), 2.64 (t, J = 6.2 Hz, 4

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H), 3.18 (s, br, 2 H), 3.65 (t, J = 6.2 Hz, 4 H); ^{13}C NMR ($CDCl_3$, 50.3 MHz): δ 29.3 (t), 30.5 (t), 34.8 (t), 60.6 (t).

1,4,8,11-Tetrathiaundecane (2.29) [5,13]

This compound was prepared according to a procedure described in literature[5,13], from **2.28** (65.1 g, 332 mmol) and thiourea (55.7 g, 732 mmol) in conc. HCl (175 mL, 1.7 mol) giving **2.29** (55%) as a colorless oil: bp 152 - 156 °C (0.35 mm Hg; rapidly distilled with a gasflame) (lit.[5] 159 - 161 °C, 0.5 mm Hg); ^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.66 - 1.88 (m, 4 H), 2.59 (t, J = 7.1 Hz, 4 H), 2.64 - 2.71 (m, 8 H); ^{13}C NMR ($CDCl_3$, 50.3 MHz): δ 24.7 (t), 29.3 (t), 30.6 (t), 36.1 (t).

(R)-(+)-2,2'-Bis(2-bromoethoxy)-1,1'-binaphthyl (2.34)

A solution of (*R*)-**2.26** (2.43 g, 4.58 mmol) and anhydrous lithium bromide (1.20 g, 13.8 mmol) in DMSO (40 mL) was stirred at 60 °C. for 20 h. Water (50 mL) was added and the mixture was extracted with Et_2O (3 x 50 mL). The combined Et_2O layers were washed with brine (75 mL), dried ($MgSO_4$) and concentrated under reduced pressure to give a yellow oil (2.25 g). The crude product was purified by column chromatography (silica gel, CH_2Cl_2) to give **2.34** (94%) as colorless crystals. Recrystallization from CH_2Cl_2/*n*-hexane afforded very long needles: mp 91.2 - 92.4 °C; $[\alpha]_D$ = + 45.6 (c = 0.296, THF), $[\alpha]_{578}$ = + 50.3, $[\alpha]_{546}$ = + 59.8, $[\alpha]_{436}$ = + 150.0, $[\alpha]_{365}$ = + 552.4; ^{1}H NMR ($CDCl_3$, 200 MHz): δ 3.31 (t, J = 6.6 Hz, 4 H), 4.21 - 4.42 (m, 4 H), 7.26 - ; ^{13}C NMR ($CDCl_3$, 50.3 MHz): δ 29.5 (t), 70.0 (t), 116.4 (d), 121.1 (s), 124.3 (d), 125.5 (d), 126.7 (d), 128.1 (d), 129.8 (d), 129.9 (s), 134.1 (s), 153.7 (s); HRMS *m/e* (M^+) calcd 497.983, obsd 497.983.

(R)-(+)-2-(3-Hydroxypropoxy)-2'hydroxy-1,1'-binaphthyl (2.35)

(R)-(+)-2,2'-Bis(3-hydroxypropoxy)-1,1'-binaphthyl (2.36)

(R)-2.35 and (R)-2.36 by alkylation of (R)-(+)-Bis-β-naphthol: (*R*)-(+)-Bis-β-naphthol (10.0 g, 35.0 mmol), 3-chloro-1-propanol (13.2 g, 100 mmol) and K_2CO_3 (19.4 g, 140 mmol) were dissolved in DMF (250 mL) and stirred at 110°C for 17 h. The reaction mixture was filtered and concentrated under reduced pressure. The residue was taken up in CH_2Cl_2 (300 mL) and washed with water (100 mL) and 4 N NaOH (2 x 150 mL). The organic layer was dried ($MgSO_4$) and concentrated under reduced pressure to give a pale yellow oil (21.05 g). The oil was heated in a bulb to bulb distillation apparatus (0.1 mm Hg, 225°C) to remove dimeric byproduct **2.37**. The residue of distillation (16.25 g) was purified by column chromatography (silica gel, Et_2O) to give the mono-alkylated product (**2.35**, 21%). Further elution (EtOAc) gave **2.36** (59%) as a white foam.

Compound **2.35**: mp 179.6 - 181.0°C; $[\alpha]_{578}$ = + 30.4 (c = 0.938, THF), $[\alpha]_{546}$ = + 39.6, $[\alpha]_{436}$ = + 152.5, $[\alpha]_{365}$ = + 843.4; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.65 - 1.71 (m, 2 H), 1.95 (s, br, 1 H), 3.28 - 3.30 (m, 2 H), 4.08 - 4.15 (m, 2 H), 5.94 (s, br, 1 H), 7.16 (d, J = 8.8 Hz, 1 H), 7.27 - 7.47 (m, 7 H), 7.92 - 7.96 (m, 3 H), 8.04 (d, J = 9.5 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 75.4 MHz): δ 31.3 (t), 59.7 (t), 67.2 (t), 114.9 (d), 116.8 (s), 117.5 (d), 123.1 (d), 124.0 (d), 124.5 (d), 124.9 (d), 126.2 (d), 126.9 (d), 127.9 (d), 128.0 (d), 128.8 (s), 129.3 (s), 129.6 (d), 130.4 (d), 133.6 (s), 133.8 (s), 151.1 (s), 154.7 (s); HRMS *m/e* (M^+) calcd 344.141, obsd 344.142.

Compound **2.36**: mp 66.3 - 68.3 °C; $[\alpha]_{589}$ = + 41.0 (c = 0.442, THF), $[\alpha]_{578}$ = + 50.2, $[\alpha]_{546}$ = + 60.9, $[\alpha]_{436}$ = + 172.0, $[\alpha]_{365}$ = + 716.1; ^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.56 - 1.80 (m, 4 H), 2.06 (s, br, 2 H), 3.29 - 3.31 (m, br, 4 H), 4.02 - 4.27 (m, 4 H), 7.13 - 7.49 (m, 8 H), 7.90 (d, J = 7.7 Hz, 2 H), 8.00 (d, J = 9.0 Hz, 2 H); ^{13}C NMR ($CDCl_3$, 50.3 MHz): δ 31.5 (t), 60.1 (t), 67.6 (t), 114.8 (d), 119.7 (s), 123.7 (d), 125.1 (d), 126.3 (d), 127.9 (d), 129.3 (s), 129.5 (d), 133.7 (s), 153.7 (s); HRMS *m/e* (M^+) calcd 402.183, obsd 402.183.

(S)-2.36 by hydrolysis of (aS)-2.38: To a stirred solution of *(aS)*-**2.38** (10.18 g, 17.9 mmol) in acetone (200 mL) at rt was added 6 N HCl (23 mL, 138 mmol). After 17 h the reaction mixture was neutralized with Na_2CO_3 and concentrated under reduced pressure. The residue was taken up

in CH_2Cl_2 (300 mL) and washed with water (2 x 150 mL) and 0.5 N NaOH (100 mL). The organic layer was dried ($MgSO_4$) and concentrated under reduced pressure to give a yellow foam (7.14 g). The crude product was purified by column chromatography (silica gel, EtOAc) to give **2.36** (95%) as a white foam: mp 66.7 - 68.2 °C; $[\alpha]_D$ = - 40.8 (c = 0.526, THF), $[\alpha]_{578}$ = - 49.7, $[\alpha]_{546}$ = - 60.4, $[\alpha]_{436}$ = - 170.7, $[\alpha]_{365}$ = - 709.2. The NMR data were in accordance with the data of the product obtained from bis-β-naphthol (vide supra).

(aS)-2,2'-Bis(3-(pyranyl-2-oxy)-propoxy)-1,1'-binaphthyl (2.38)

(*S*)-(-)-Bis-β-naphthol (5.72 g, 20.0 mmol), 2-(3-chloro-1-propoxy)-pyran[98] (7.50 g, 42.0 mmol) and K_2CO_3 (5.80 g, 42 mmol) were dissolved in DMF (150 mL) and stirred at 110°C for 4 h. The reaction mixture was concentrated under reduced pressure, the residue was taken up in CH_2Cl_2 (200 mL) and washed with water 2 x 150 mL), 2 N NaOH (2 x 150 mL) and brine (150 mL). The organic layer was dried ($MgSO_4$) and concentrated under reduced pressure to give a brown oil (10.61 g). The crude product was purified by column chromatography (silica gel, Et_2O) to give **2.38** (89%) as a yellow oil: ^1H NMR ($CDCl_3$, 300 MHz): δ 1.38 - 1.78 (m, 16 H), 2.87 - 3.06 (m, 2 H), 3.33- 3.45 (m, 4 H), 3.65 - 3.75 (m, 2 H), 4.03 - 4.16 (m, 5 H), 4.28 - 4.31 (m, 1 H), 7.15 - 7.47 (m, 8 H), 7.88 (d, J = 8.1 Hz, 2 H), 7.96 (d, J = 9.2 Hz, 2 H); ^{13}C NMR ($CDCl_3$, 75.4 MHz): δ 19.4 (t), 19.6 (t), 25.3 (t), 29.5 (t), 29.6 (t), 30.4 (t), 61.9 (t), 62.0 (t), 62.1 (t), 63.6 (t), 63.7 (t), 63.8 (t), 66.2 (t), 66.3 (t), 66.4 (t), 98.6 (d), 98.7 (d), 115.4 (d), 120.2 (s), 120.3 (s), 123.2 (d), 123.3 (d), 125.2 (d), 125.2 (d), 125.9 (d), 127.6 (d), 127.6 (d), 128.9 (d), 129.0 (s), 133.9 (s), 154.0 (s), 154.1 (s); HRMS *m/e* (M^+) calcd 570.298, obsd 570.298.

2,2'-Bis(3-bromopropoxy)-1,1'binaphthyl (2.39)

(S)-2.39 From 2.38: Triphenylphosphine (21.2 g, 81 mmol) was dissolved in CH_2Cl_2 (150 mL) and cooled to 0°C. Bromine (4.14 mL, 81 mmol) was slowly added initially forming a white precipitate that turns orange upon further adding. When all the bromine was added the reaction mixture was stirred at 0°C for 45 min. A solution of **2.38** (8.6 g, 15.1 mmol) in CH_2Cl_2 (30 mL) was added in 15 min at 0°C and the reaction mixture was stirred at room temperature for 17 h. CH_2Cl_2 (100 mL) was added and the reaction mixture was washed twice with water. The organic layer was dried ($MgSO_4$) and concentrated under reduced pressure to give a light brown solid (22.25 g). The solid was recrystallized from toluene/n-octane to give white crystals (7.28 g, triphenylphosphineoxide). The mother liquor was concentrated under reduced pressure and purified by column chromatography (silica gel, CH_2Cl_2/n-hexane 1:1) to give a yellowish brown oil (7.00 g). This oil was boiled in methanol and decanted while hot. The decantate was concentrated under reduced pressure to give **2.39** (73%) as a yellow oil. Analytically pure material was obtained by additional column chromatography (silica gel, toluene) to give **2.39** as a colorless oil: $[\alpha]_D$ = - 46.5 (c = 0.400, THF), $[\alpha]_{578}$ = - 49.8, $[\alpha]_{546}$ = - 59.8, $[\alpha]_{436}$ = - 145.5, $[\alpha]_{365}$ = - 442.0; ^1H NMR ($CDCl_3$, 300 MHz): δ 1.92 - 1.99 (m, 4 H), 2.84 - 3.02 (m, 4 H), 4.06 - 4.20 (m, 4 H), 7.22 - 7.48 (m, 8 H), 7.92 (d, J = 8.1 Hz, 2 H), 8.00 (d, J = 9.2 Hz, 2 H); ^{13}C NMR ($CDCl_3$, 75.4 MHz): δ 30.0 (t), 32.4 (t), 66.8 (t), 115.3 (d), 120.3 (s), 123.6 (d), 125.2 (d), 126.3 (d), 127.7 (d), 129.2 (s), 129.3 (d), 133.8 (s), 153.7 (s); HRMS *m/e* (M^+) calcd 526.014, obsd 526.013; Anal. Calcd (found) for $C_{26}H_{24}O_2Br_2$: C, 59.11 (59.19); H, 4.58 (4.58); Br, 30.25 (30.15).

(R)-2.39 from 2.36: Compound **2.36** (7.93 g, 19.7 mmol) was dissolved in THF (150 mL). Pyridine (0.61 mL, 7.5 mmol) was added and the reaction mixture was cooled to 0°C. Phosphorus tribromide (2.0 mL, 21.3 mmol) was added in 5 min giving a white precipitate. The reaction mixture was allowed to warm to room temperature. After stirring at ambient temperature for 20 h the reaction mixture was concentrated under reduced pressure. The residue was taken up in benzene (100 mL) and water (150 mL). The benzene layer was separated and the water layer was extracted with benzene (2 x 75 mL). The combined organic layers were dried ($MgSO_4$) and concentrated under reduced pressure to give a yellow oil (16.17 g). The crude product was purified by column chromatography (silica gel, toluene) to give **2.39** (19%) as a colorless oil: $[\alpha]_D$

= + 46.0 (c = 0.544, THF), $[\alpha]_{578}$ = + 49.1, $[\alpha]_{546}$ = + 58.9, $[\alpha]_{436}$ = +144.0, $[\alpha]_{365}$ = + 436.9; ^{1}H NMR and ^{13}C NMR spectra were identical to the spectra of (*S*)-**2.39** obtained from **2.38**.

1,7-Dihydroxy-4-thiaheptane[99]

The literature procedure[99] was improved: a solution of $Na_2S{\cdot}3H_2O$ (6.62 g, 50 mmol) in 3-chloro-1-propanol (8.4 mL, 100 mmol) was refluxed for 18 h. The crude reaction mixture was distilled (140 °C, 0.3 mm Hg) to give the product (66%) as a colorless oil: ^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.77 - 1.90 (m, 4 H), 2.64 (t, J = 7.1 Hz, 4 H), 2.82 (s, br, 2 H), 3.72 (t, br, J = 5.9 Hz, 4 H); ^{13}C NMR ($CDCl_3$, 50.3 MHz): δ 28.6 (t), 31.9 (t), 61.4 (t).

1,5,9-Trithianonane (2.40)[100]

This compound was prepared according to the literature procedure[100], from 1,7-dihydroxy-4-thiaheptane (vide supra) (4.95 g, 33.0 mmol) and thiourea (5.60 g, 72.9 mmol) to give **2.40** (54%) as a colorless oil: ^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.36 (t, J = 8.1 Hz, 2 H), 1.78 - 1.95 (m, 4 H), 2.55 - 2.66 (m, 8 H); ^{13}C NMR ($CDCl_3$, 50.3 MHz): δ 23.4 (t), 30.2 (t), 33.2 (t).

2-(Mercaptomethyl)-1-propene-3-thiol (2.43)[89]

This compound was prepared according to a procedure described in the literature[89], from 3-chloro-2-(chloromethyl)-1-propene (10.0 mL, 86 mmol), sodium (4.6 g, 200 mmol) and freshly distilled thiolacetic acid (14.0 mL, 200 mmol) to give **2.43** (66%) as a pale yellow oil: bp 95°C (22 mm Hg) (lit.[89] 44-46°C, 0.3 Torr); ^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.49 (t, J = 8.1 Hz, 2 H), 3.33 (d, J = 8.1 Hz, 4 H), 4.97 (s, 2 H); ^{13}C NMR ($CDCl_3$, 50.3 MHz): δ 28.1 (t), 113.3 (t), 114.9 (s).

1,2-Di-(mercaptomethyl)benzene (2.45)[91]

This compound was prepared according to a procedure described in the literature[91], from α,α'-dibromo-*o*-xylene (10.0 g, 37.9 mmol), and thiourea (5.77 g, 75.8 mmol) to give **2.45** (94%) as a white solid: mp 42-45°C (lit.[91] 41-44°C); ^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.89 (t, J = 7.1 Hz, 2 H), 3.88 (d, J = 7.1 Hz, 4 H), 7.21 - 7.33 (m, 4 H); ^{13}C NMR ($CDCl_3$, 50.3 MHz): δ 26.1 (t), 127.9 (d), 129.8 (d), 138.7 (s).

Synthesis of thiocrown ethers

(S)-(-)-2,3:4,5-Di(1,2-naphtho)-1,6-dioxa-9,13-dithiacyclopentadeca-2,4-diene (2.30)
(Typical procedure)

A solution of (*S*)-**2.26** (2.65 g, 5.0 mmol) and 1,3-propanedithiol (0.51 g, 5.1 mmol) in DMF (150 mL) was added dropwise to a stirred suspension of Cs_2CO_3 (3.43 g, 10.5 mmol) in DMF (600 mL) at 60°C over a period of 10 - 18 h. The reaction mixture was filtered and concentrated under reduced pressure. The residue was taken up in CH_2Cl_2 (100 mL) and washed with water (2 x 100 mL) and 2 N NaOH (2 x 100 mL). The organic layer was dried ($MgSO_4$) and concentrated under reduced pressure to give a yellow foam (2.64 g). The crude product was purified by column chromatography (silica gel, toluene) to give **2.30** (30 %) as a white foam: mp 64.2 - 64.6°C; $[\alpha]_{578}$ = - 201.9 (c = 1.054, THF), $[\alpha]_{546}$ = - 238.4, $[\alpha]_{436}$ = - 530.8, $[\alpha]_{365}$ = - 1596; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.73 - 1.88 (m, 2 H), 2.44 - 2.68 (m, 8 H), 4.08 - 4.20 (m, 4 H), 7.15 - 7.47 (m, 8 H), 7.89 (d, J = 7.7 Hz, 2 H), 7.98 (d, J = 8.8 Hz, 2 H); ^{13}C NMR ($CDCl_3$, 75.4 MHz): δ 30.0 (t), 30.3 (t), 31.2 (t), 70.5 (t), 116.8 (d), 121.2 (s), 123.8 (d), 125.3 (d), 126.2 (d), 127.8 (d), 129.3 (d), 129.6 (s), 133.9 (s), 154.1 (s); HRMS *m/e* (M^+) calcd 446.137, obsd

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446.136.
(R)-2.30 from (R)-2.34 and 1,3-propanedithiol: Reaction of (*R*)-**2.34** (500 mg, 1.00 mmol) and 1,3-propanedithiol (100 mg, 1.00 mmol) afforded (*R*)-**2.30** in 31% yield: mp 64.3 - 64.6 °C; $[\alpha]_{578}$ = + 204.8 (c = 0.968, THF), $[\alpha]_{546}$ = + 242.0, $[\alpha]_{436}$ = + 538.0, $[\alpha]_{365}$ = + 1624.

(S)-(-)-2,3:4,5-Di(1,2-naphtho)-1,6-dioxa-9,12-dithiacyclotetradeca-2,4-diene (2.31)
From (*S*)-**2.26** and 1,2-ethanedithiol: yield: 32%; mp 75.7 - 76.2 °C; $[\alpha]_{578}$ = - 153.5 (c = 0.998, THF), $[\alpha]_{546}$ = - 183.0, $[\alpha]_{436}$ = - 444.6, $[\alpha]_{365}$ = - 1576; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 2.47 - 2.88 (m, 8 H), 4.06 - 4.41 (m, 4 H), 7.12 - 7.53 (m, 8 H), 7.90 (d, J = 8.1 Hz, 2 H), 7.99 (d, J = 8.8 Hz, 2 H); ^{13}C NMR ($CDCl_3$, 75.4 MHz): δ 30.2 (t), 31.5 (t), 72.3 (t), 117.3 (d), 121.3 (s), 124.0 (d), 125.1 (d), 126.3 (d), 127.8 (d), 129.4 (d), 129.7 (s), 133.8 (s), 153.9 (s); HRMS *m/e* (M^+) calcd 432.122, obsd 432.122.
(R)-(+)-2.31 Yield: 30 %; mp 74.8 - 75.9 °C; $[\alpha]_{578}$ = + 156.6 (c = 0.554, THF), $[\alpha]_{546}$ = + 186.4, $[\alpha]_{436}$ = + 455.0, $[\alpha]_{365}$ = + 1612.
(R)-2.31 from (R)-2.34 and 1,2-ethanedithiol: yield: 33%; mp 75.4 - 76.4 °C; $[\alpha]_{578}$ = + 156.0 (c = 0.660, THF), $[\alpha]_{546}$ = + 186.1, $[\alpha]_{436}$ = + 455.1, $[\alpha]_{365}$ = + 1608.

(R)-(+)-2,3:4,5-Di(1,2-naphtho)-1,6-dioxa-9,12,15-trithiacycloheptadeca-2,4-diene (2.32)
From (*R*)-**2.26** and 1,4,7-trithiaheptane: yield: 58%; mp 54.3 - 56.1°C; $[\alpha]_{578}$ = + 90.7 (c = 1.060, THF), $[\alpha]_{546}$ = + 109.6, $[\alpha]_{436}$ = + 283.8, $[\alpha]_{365}$ = + 1065; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 2.28 - 2.97 (m, 12 H), 3.85 - 4.02 (m, 4 H), 6.97 - 7.32 (m, 8 H), 7.72 (d, J = 8.0 Hz, 2 H), 7.81 (d, J = 8.8 Hz, 2 H); ^{13}C NMR ($CDCl_3$, 75.4 MHz): δ 30.9 (t), 31.2 (t), 32.2 (t), 71.4 (t), 116.6 (d), 121.0 (s), 123.9 (d), 125.3 (d), 126.3 (d), 127.8 (d), 129.5 (d), 129.6 (s), 133.9 (s), 153.9 (s); HRMS *m/e* (M^+) calcd 492.125, obsd 492.126; Anal. Calcd (found) for $C_{28}H_{28}O_2S_3$: C, 68.26 (67.83); H, 5.73 (5.69); S, 19.52 (19.24).
(S)-2.32 from (S)-2.26 and 1,4,7-trithiaheptane: yield: 52%; mp 54.8 - 56.1°C; $[\alpha]_{578}$ = - 91.7 (c = 0.542, THF), $[\alpha]_{546}$ = - 110.6, $[\alpha]_{436}$ = - 287.2, $[\alpha]_{365}$ = - 1081; e.e. > 99.5 % as determined by HPLC[101].

(R)-(+)-2,3:4,5-Di(1,2-naphtho)-1,6-dioxa-9,12,16,19-tetrathiacyclouneicosa-2,4-diene (2.33)
From (*R*)-**2.26** and **2.29**: yield: 54% as a colorless oil; $[\alpha]_D$ = + 130.3 (c = 0.284, THF), $[\alpha]_{578}$ = + 141.9, $[\alpha]_{546}$ = + 168.0, $[\alpha]_{436}$ = + 376.1, $[\alpha]_{365}$ = + 1081; ^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.86 (quintet, J = 6.8 Hz, 2 H), 2.39 - 2.74 (m, 16 H), 4.05 - 4.35 (m, 4 H), 7.16 - 7.50 (m, 8 H), 7.90 (d, J = 7.8 Hz, 2 H), 8.00 (d, J = 9.0 Hz, 2 H); ^{13}C NMR ($CDCl_3$, 50.3 MHz): δ 29.8 (t), 30.6 (t), 31.2 (t), 32.4 (t), 32.5 (t), 70.5 (t), 115.7 (d), 120.7 (s), 124.0 (d), 125.4 (d), 126.5 (d), 127.9 (d), 129.6 (d), 134.1 (s), 153.9 (s); HRMS *m/e* (M^+) calcd 566.144, obsd 566.144.

(S)-(-)-2,3:4,5-Di(1,2-naphtho)-1,6-dioxa-10,14-dithiacycloheptadeca-2,4-diene (2.41)
From (*S*)-**2.39** and 1,3-propanedithiol: yield: 61%; mp 107.6 - 109.9 °C; $[\alpha]_{578}$ = - 163.7 (c = 1.098, THF), $[\alpha]_{546}$ = - 193.8, $[\alpha]_{436}$ = - 446.2, $[\alpha]_{365}$ = - 1433; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.69 - 1.78 (m, 6 H), 2.25 - 2.40 (m, 4 H), 2.53 (t, J = 7.0 Hz, 4 H), 3.83 - 3.90 (m, 2 H), 4.27 - 4.34 (m, 2 H), 7.10 - 7.47 (m, 8 H), 7.88 (d, J = 8.0 Hz, 2 H), 7.96 (d, J = 8.8 Hz, 2 H); ^{13}C NMR ($CDCl_3$, 70.4 MHz): δ 27.6 (t), 29.3 (t), 29.6 (t), 30.4 (t), 67.5 (t), 115.5 (d), 120.4 (s), 123.4 (d), 125.2 (d), 126.1 (d), 127.7 (d), 129.1 (d), 129.2 (s), 134.0 (s), 154.1 (s); HRMS *m/e* (M^+) calcd 474.169, obsd 474.169.

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101 A water cooled DAICEL OT$^+$ column was used (see ref. 96), with *n*-hexane/*i*-propanol 9:1 as eluent (flow 1.0 mL/min); a solution of **2.32** in *i*-propanol was injected: retention times (*S*)-**2.32**: 28.3 min; (*R*)-**2.32**: 48.0 min.

(S)-(-)-2,3:4,5-Di(1,2-naphtho)-1,6-dioxa-10,14,18-trithiacyclouneicosa-2,4-diene (2.42)
From (*S*)-**2.39** and **2.40**: yield: 47% as a colorless oil; $[\alpha]_D$ = - 130.7 (c = 0.668, THF), $[\alpha]_{578}$ = - 142.2, $[\alpha]_{546}$ = - 167.4, $[\alpha]_{436}$ = - 368.1, $[\alpha]_{365}$ = - 1060; ^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.73 - 1.94 (m, 8 H), 2.32 (t, J = 7.1 Hz, 4 H), 2.48 - 2.63 (m, 4 H), 2.68 (t, J = 7.1 Hz, 4 H), 3.97 - 4.07 (m, 2 H), 4.19 - 4.30 (m, 2 H), 7.22 - 7.45 (m, 6 H), 7.54 (d, J = 9.0 Hz, 2 H), 7.96 (d, J = 7.8 Hz, 2 H), 8.04 (d, J = 9.0 Hz, 2 H); ^{13}C NMR ($CDCl_3$, 50.3 MHz): δ 28.3 (t), 29.4 (t), 29.7 (t), 30.3 (t), 30.8 (t), 68.0 (t), 115.8 (d), 120.6 (s), 123.7 (d), 125.5 (d), 126.4 (d), 128.0 (d), 129.4 (d), 129.5 (s), 134.2 (s), 154.3 (s); HRMS *m/e* (M^+) calcd 548.188, obsd 548.188.

(S)-(-)-2,3:4,5-Di(1,2-naphtho)-1,6-dioxa-9,13-dithia-11-methylene-cyclopentadeca-2,4-diene-(2.46)
From (*S*)-**2.26** and **2.43**: yield: 20%; mp 54.5 - 55.6°C; $[\alpha]_{578}$ = - 176.6 (c = 0.988, THF), $[\alpha]_{546}$ = - 208.8, $[\alpha]_{436}$ = - 468.6, $[\alpha]_{365}$ = - 1423; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 2.55 - 2.68 (m, 4 H), 3.28 (AB system, J_1 = 62.6 Hz, J_2 = 13.9 Hz, 4 H), 4.15 - 4.31 (m, 4 H), 5.08 (s, 2 H), 7.17 - 7.43 (m, 8 H), 7.91 (d, J = 8.1 Hz, 2 H), 7.99 (d, J = 9.2 Hz, 2 H); ^{13}C NMR ($CDCl_3$, 75.4 MHz): δ 31.4 (t), 36.4 (t), 69.3 (t), 114.8 (t), 115.1 (d), 120.2 (s), 123.5 (d), 125.2 (d), 126.2 (d), 127.8 (d), 129.2 (d), 134.0 (s), 142.6 (s), 153.8 (s); HRMS *m/e* (M^+) calcd 458.137, obsd 458.136.

(S)-(-)-2,3:4,5-Di(1,2-naphtho)-1,6-dioxa-10,14-dithia-12-methylene-cycloheptadeca-2,4-diene (2.47)
From (*S*)-**2.39** and **2.43**: yield: 68%; mp 69.8 - 70.4 °C; $[\alpha]_{578}$ = - 138.5 (c = 0.960, THF), $[\alpha]_{546}$ = - 165.6, $[\alpha]_{436}$ = - 399.1, $[\alpha]_{365}$ = - 1377; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.72 - 1.87 (m, 4 H), 2.23 - 2.45 (m, 4 H), 3.22 (AB system, J_1 = 24.0 Hz, J_2 = 14.5 Hz, 4 H), 3.86 - 3.93 (m, 2 H), 4.20 - 4.27 (m, 2 H), 5.04 (s, 2 H), 7.09 - 7.45 (m, 8 H), 7.87 (d, J = 8.1 Hz, 2 H), 7.96 (d, J = 9.2 Hz, 2 H); ^{13}C NMR ($CDCl_3$, 70.4 MHz): δ 28.5 (t), 29.2 (t), 36.2 (t), 67.7 (t), 114.8 (t), 115.2 (d), 120.1 (s), 123.4 (d), 125.1 (d), 126.1 (d), 127.7 (d), 129.0 (d), 129.1 (s), 134.0 (s), 140.9 (s), 153.9 (s); HRMS *m/e* (M^+) calcd 486.169, obsd 486.169.

(R)-(+)-2,3:4,5-Di(1,2-naphtho)-1,6-dioxa-9,12-dithia-10,11-(1,2-benzo)cyclotetradeca-2,4-diene (2.48)
From (*R*)-**2.34** and **2.44**: yield: 72%; mp 222.2 - 223.9 °C; $[\alpha]_D$ = + 345.6 (c = 0.544, THF), $[\alpha]_{578}$ = + 381.6, $[\alpha]_{546}$ = + 448.9, $[\alpha]_{436}$ = + 981.8, $[\alpha]_{365}$ = + 2873; ^{1}H NMR ($CDCl_3$, 200 MHz): δ 2.94 - 3.09 (m, 2 H), 3.18 - 3.30 (m, 2 H), 4.13 - 4.33 (m, 4 H), 7.06 - 7.47 (m, 12 H), 7.86 (d, J = 8.0 Hz, 2 H), 7.92 (d, J = 9.0 Hz, 2 H); ^{13}C NMR ($CDCl_3$, 50.3 MHz): δ 34.8 (t), 67.6 (t), 100.1 (s), 115.5 (d), 120.1 (s), 123.6 (d), 125.4 (d), 126.3 (d), 127.7 (d), 127.8 (d), 129.3 (s), 129.3 (s), 133.4 (d), 134.1 (s), 138.6 (s), 154.0 (s); HRMS *m/e* (M^+) calcd 480.122, obsd 480.122.

(S)-(-)-2,3:4,5-Di(1,2-naphtho)-1,6-dioxa-10,15-dithia-12,13-(1,2-benzo)-cyclooctadeca-2,4-diene (2.49)
From (*S*)-**2.39** and **2.45**: yield: 61%; mp 75.9 - 77.8 °C; $[\alpha]_D$ = - 160.8 (c = 0.306, THF), $[\alpha]_{578}$ = - 177.8, $[\alpha]_{546}$ = -210.8, $[\alpha]_{436}$ = - 491.5, $[\alpha]_{365}$ = - 1587; ^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.85 - 2.02 (m, 4 H), 2.44 - 2.67 (m, 4 H), 3.98 (AB-system, J_1 = 62.0 Hz, J_2 = 12.0 Hz, 4 H), 3.97 - 4.08 (m, 2 H), 4.35 - 4.47 (m, 2 H), 7.34 - 7.51 (m, 10 H), 7.54 (d, J = 9.0 Hz, 2 H), 8.03 (d, J = 8.1 Hz, 2 H), 8.09 (d, J = 9.0 Hz, 2 H); ^{13}C NMR ($CDCl_3$, 50.3 MHz): δ 29.3 (t), 29.6 (t), 34.4 (t), 67.6 (t), 115.2 (d), 120.4 (s), 123.7 (d), 125.5 (d), 126.5 (d), 127.8 (d), 128.1 (d), 129.4 (s), 129.5 (d), 130.6 (d), 134.4 (s), 136.4 (s), 154.1 (s); HRMS *m/e* (M^+) calcd 536.184, obsd 536.184.

(R)-(+)-2,3:4,5-Di(1,2-naphtho)-1,6-dioxa-9,13-dithia-11,11-dimethylcyclotetradeca-2,4-diene (2.53)
From (*R*)-**2.26** and **2.52**: yield: 37%; mp 89.2 - 89.9 °C; $[\alpha]_D$ = + 257.6 (c = 0.304, THF), $[\alpha]_{578}$ = + 286.2, $[\alpha]_{546}$ = + 335.2, $[\alpha]_{436}$ = + 716.1, $[\alpha]_{365}$ = + 1981; ^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.05 (s, 6 H), 2.36 (d, J = 12.6 Hz, 2 H), 2.48 - 2.60 (m, 2 H), 2.78 (d, J = 12.6 Hz, 2 H), 2.71 - 2.96 (m, 2 H), 4.12 - 4.30 (m, 4 H), 7.21 - 7.50 (m, 8 H), 7.93 (d, J = 7.7 Hz, 2 H), 8.02 (d, J = 9.0 Hz, 2 H); ^{13}C NMR ($CDCl_3$, 50.3 MHz): δ 27.8 (q), 31.6 (t), 36.4 (s), 41.1 (t), 68.0 (t), 115.7 (d), 123.7 (d), 125.5 (d), 126.4 (d), 128.0 (d), 128.0 (s), 129.4 (d), 134.2 (s), 153.8 (s); HRMS *m/e* (M^+) calcd 474.169, obsd 474.169.

(S)-(-)-2,3:4,5-Di(1,2-naphtho)-1,6-dioxa-10,14-dithia-12,12-dimethylcycloheptadeca-2,4-diene (2.54)
From (*S*)-**2.39** and **2.52**: yield: 24%; mp 174.6 - 176.6 °C; $[\alpha]_D$ = - 145.3 (c = 0.298, THF), $[\alpha]_{578}$ = - 159.7, $[\alpha]_{546}$ = - 189.3, $[\alpha]_{436}$ = - 434.6, $[\alpha]_{365}$ = - 1427; ^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.03 (s, 6 H), 1.72 - 1.85 (m, 4 H), 2.34 - 2.72 (m, 8 H), 3.88 - 3.98 (m, 2 H), 4.22 - 4.34 (m, 2 H), 7.13 - 7.39 (m, 6 H), 7.47 (d, J = 8.9 Hz, 2 H), 7.90 (d, J = 7.7 Hz, 2 H), 7.98 (d, J = 8.9 Hz, 2 H); ^{13}C NMR ($CDCl_3$, 50.3 MHz): δ 27.6 (q), 29.3 (t), 29.5 (t), 35.9 (s), 42.9 (t), 67.4 (t), 115.2 (d), 120.2 (s), 123.4 (d), 125.3 (d), 126.2 (d), 127.9 (d), 129.1 (s), 129.2 (d), 134.1 (s), 154.2 (s); HRMS *m/e* (M^+) calcd 502.200, obsd 502.200.